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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/811,123
Filing Date	March 16, 2001
First Named Inventor	Sharon ERICKSON, et al.
Group/Art Unit	1642
Examiner Name	SANG, Hong
Attorney Docket Number	39766-0073 A2

Total Number of Pages in This Submission

ENCLOSURES *(check all that apply)*

- ☒ **Fee Transmittal Form**
  - ☐ Fee Attached
- Amendment / Response
  - ☐ After Final
  - ☐ Version With Markings Showing Changes
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
  - ☐ Copy of Notice
- ☐ Copy of an Assignment
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, by Assignee to Exclusion of Inventor Under 37 C.F.R. §3.71 With Revocation of Prior Powers
- ☐ Terminal Disclaimer
- ☐ Small Entity Statement
- ☐ Request for Refund
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ **Appeal Communication to Group** ***(Appeal Notice, Brief, Reply Brief)***
- ☐ Request for Oral Hearing
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- ☒ **ADDITIONAL ENCLOSURE(S)** ***(PLEASE IDENTIFY BELOW):***
- ☒ **EVIDENCE APPENDIX ITEMS 1-2; RETURN POSTCARD.**

Remarks

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SIGNATURE OF APPLICANT, ATTORNEY OR AGENT

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Date	February 23, 2006	Customer Number:	25213

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FEE TRANSMITTAL for FY 2006

Effective 12/08/2004. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) **500**

Complete if Known	
Application Number	**09/811,123**
Filing Date	**March 16, 2001**
First Named Inventor	**Sharon ERICKSON, et al.**
Examiner Name	**SANG, Hong**
Art Unit	**1642**
Attorney Docket No.	**39766-0073 A2**

METHOD OF PAYMENT (check one)

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Deposit Account Number: **08-1641** (Docket No. **39766-0073 A2**)

Deposit Account Name: Heller Ehrman LLP

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FEE CALCULATION

1. BASIC FILING FEE

Large Fee Code	Large Fee ($)	Small Fee Code	Small Fee ($)	Fee Description	Fee Paid
1001	300	2001	150	Utility filing fee	
1002	350	2002	175	Design filing fee	
1003	550	2003	275	Plant filing fee	
1004	790	2004	395	Reissue filing fee	
1005	200	2005	100	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		x		=
Independent Claims		-3** =		x		= 0
Multiple Dependent						= 0

Large Fee Code	Large Fee ($)	Small Fee Code	Small Fee ($)	Fee Description
1202	50	2202	25	Claims in excess of 20
1201	200	2201	100	Independent claims in excess of 3
1203	360	2203	180	Multiple dependent claim, if not paid
1204	200	2204	100	**Reissue independent claims over original patent
1205	50	2205	25	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Large Fee ($)	Small Fee Code	Small Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	120	2251	60	Extension for reply within first month	
1252	450	2252	225	Extension for reply within second month	
1253	1,020	2253	510	Extension for reply within third month	
1254	1,590	2254	795	Extension for reply within fourth month	
1255	2,160	2255	1,080	Extension for reply within fifth month	
1401	500	2401	250	Notice of Appeal	
1402	500	2402	250	Filing a brief in support of an appeal	500.00
1403	1,000	2403	500	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	500	2452	250	Petition to revive - unavoidable	
1453	1,500	2453	750	Petition to revive - unintentional	
1501	1,400	2501	700	Utility issue fee (or reissue)	
1502	800	2502	400	Design issue fee	
1503	1,100	2503	550	Plant issue fee	
1460		1460		Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

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SUBTOTAL (3) ($)500

SUBMITTED BY

Complete *(if applicable)*

Name *(Print/Type)*	James A. Fox	Registration No. *(Attorney/Agent)*	38,455	*Telephone*	650-324-7000
Signature		*Date*	February 23, 2006	Customer No.	25213

OIPE
FEB 23 2006
PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	) Examiner: SANG, Hong
Sharon ERICKSON, et al.	) Art Unit: 1642
Application Serial No. 09/811,123	) Confirmation No. 6508
Filed: March 16, 2001	) Attorney's Docket No. 39766-0073 A2
For: **METHODS OF TREATMENT USING ANTI-ErbB ANTIBODY-MAYTANSINOID CONJUGATES**	) **Customer No. 25213**

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DATE MAILED: FEBRUARY 23, 2006

ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANTS' BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On November 2, 2005, the Patent and Trademark Office made a final rejection to pending Claims 2, 4-6, 8-21, 24-48 and 55 of the above-named patent application. In response to that Final Office Action, an Amendment After Final was mailed on December 23, 2005, and entered per an Advisory Action mailed January 23, 2006, amending the priority claim to cite the conversion of parent United States Patent Application Serial No. 09/602,530, filed June 23, 2000, to United States Provisional Patent Application Serial No. 60/327,563. A Notice of Appeal was filed on January 26, 2006 appealing the rejections of Claims 2, 4-6, 8-21, 24-48 and 55.

Appellants hereby appeal to the Board of Patent Appeals and Interferences from the last decision of the PTO. The present appeal brief is filed within the two month shortened statutory period following the filing of a Notice of Appeal for filing an Appeal Brief, and is believed to be timely filed. The following constitutes Appellants' Brief on Appeal.

1. REAL PARTY IN INTEREST

The real parties in interest are Genentech, Inc., South San Francisco, California, by an assignment of the patent application U.S. Patent Application Serial No. 09/811,123 recorded July 19, 2001, at Reel 011977 and Frame 0409, and ImmunoGen Inc., of Cambridge, Massachusetts, by an assignment of the patent application U.S. Patent Application Serial No. 09/811,123 recorded on April 4, 2003, at Reel 013566 and Frame 0732 and also recorded December 20, 2002, at Reel 013640 and Frame 0657.

2. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

3. STATUS OF CLAIMS

Claims 2, 4-6, 8-21, 24-48 and 55 are in this application.

Claims 1, 3, 7, 22-23, and 49-54 are canceled.

Claims 2, 4-6, 8-21, 24-48 and 55 stand rejected and Appellants appeal the rejection of these claims.

A copy of the rejected claims involved in the present Appeal is provided as the Claims Appendix.

4. STATUS OF AMENDMENTS

The priority claim stands as amended in the amendment filed December 23, 2005 and entered per the Advisory Action mailed January 23, 2006. Claims 5, 6, 14, 18 and 55 were amended in the Amendment and Response submitted on September 8, 2005, and entered per the final Office Action mailed on November 2, 2005. Accordingly, Claims 2, 4-6, 8-21, 24-48 and 55 stand as amended on September 8, 2005.

5. SUMMARY OF THE CLAIMED SUBJECT MATTER

The invention claimed in the present application is related to methods for treating a tumor in a mammal, comprising the steps of (i) identifying a tumor that overexpresses an ErbB2 receptor that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells, and

(ii) administering to a mammal having such a tumor a therapeutically effective amount of a conjugate of an anti-ErbB2 antibody which binds to the 4D5 epitope with a maytansinoid. In more detailed embodiments, the invention further provides that the antibody may be a growth inhibitory antibody, may induce cell death, or may induce apoptosis. The tumors may be cancer, including breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate and bladder cancer. The antibodies may have biological characteristics of a 4D5 monoclonal antibody (ATCC CRL 10463), or may bind the same epitope as this antibody, may be humanized, including may be huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, or huMab4D5-8, and may be antibody fragments. The maytansinoid may be a maytansinol ester, may be DM1 as illustrated in the claims, and may be linked by specific linkers named in the claims. The conjugate may have multiple maytansinoid molecules per antibody molecule. The methods may include administration of a second antibody (which may be conjugated with a cytotoxic agent), different identified doses of the conjugates, different identified dosing schedules, and may improve the objective response rate, the duration of response, and may increase survival compared with treatment by huMab4D5-8 alone.

Thus, the claimed methods require at least the steps of identifying the tumors to be treated by the claimed methods, and treating them with the particular antibody-drug conjugates specified in the claim. The prior art lacked any teaching or suggestion of the complete invention, including the combination of the steps of identifying the tumors to be treated and of treating the tumors as claimed, once identified. The claimed invention provides a method for treating a particular population of tumors for which the proper treatment was previously unknown. The present inventors were the first to recognize that this particular population of tumors could be treated with the particular antibody-drug conjugates recited in the claimed methods. No prior suggestion or teaching indicated that the proper treatment required that the tumors first be identified as falling within the population of tumors as recited in the claims and then be treated as claimed, nor that these particular tumors could be successfully treated by the methods of the claimed invention.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Whether Claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41 are patentable under 35 U.S.C. §103(a) over Chari et al. (U.S. Patent 5,208,020; hereafter "Chari") in view of Hudziak (U.S. Patent 5,725,856; hereafter "Hudziak") and further in view of Lewis (Lewis, G.D. et al., J. Immunol., hereafter "Lewis").

II. Whether Claims 55, 2, 4, 5, 8-21, 24-33, 38-41, and 46-48 are patentable under 35 U.S.C. §103(a) over Chari in view of Carter (U.S. Patent 6,054,297, hereafter "Carter") and further in view of Lewis.

III. Whether Claims 55, 2, 4-6, 8-12, 14, 20, 24-33, and 38-41 are patentable under 35 U.S.C. §103(a) over Chari in view of Bacus (U.S. Patent 5,514,554, hereafter "Bacus") and further in view of Lewis.

IV. Whether Claims 55, 2, 8-14, 20, and 24-33 are patentable under 35 U.S.C. §103(a) over Chari in view of Huston et al. (U.S. Patent 5,877,305, hereafter "Huston") and further in view of Lewis.

V. Whether Claims 55, 2, 8-12, 24-33, and 38-41 are patentable under 35 U.S.C. §103(a) over Chari in view of King (U.S. Patent 5,747,261, hereafter "King") and further in view of Lewis.

VI. Whether Claims 55, 34, 44, and 45 are patentable under 35 U.S.C. §103(a) over Chari in combination with Hudziak, Bacus, Huston or King in view of Lewis and further in view of Senger (U.S. Patent 6,022,541, hereafter "Senger").

VII. Whether Claims 55, 34-37, 42, and 43 are patentable under 35 U.S.C. §103(a) over Chari in combination with Hudziak, Bacus, Huston or King in view of Lewis and further in view of Sliwkowski et al. (J. Biol. Chem. 269:14661-14665 (1994), hereafter "Sliwkowski") or Carter.

VIII. Whether Claims 55, 4-6, 8-19, 24, 25, 27, and 32 are patentable under 35 U.S.C. §103(a) over Iwassa (U.S. Patent 5,217,713, hereafter "Iwassa") in combination with Carter, Hudziak, Bacus, Huston, or King, in view of Lewis.

IX. Whether Claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41 are patentable under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over claims 13-18 of Chari, U.S. Patent 5,208,020 in view of Hudziak and further in view of Lewis.

7. ARGUMENT

The claims stand rejected under two theories of obviousness, under 35 U.S.C. § 103(a) as allegedly obvious over a variety of combinations of cited references (Issues I-VIII) and as allegedly obvious under the judicially created doctrine of obviousness double patenting over references that include a reference in which one of the inventors of the present application is also an inventor (Issue IX). For the sake of clarity, Appellants summarize the arguments regarding the rejections in the section entitled *Summary of the Arguments*, and then, following this introductory section, the individual grounds for rejection alleged by the Office are each addressed in turn in the section entitled *Detailed Arguments*.

In addition, Appellants submit two Declarations which were submitted with the response received at the United States Patent and Trademark Office (USPTO) on September 8, 2005. One of the Declarants is an inventor of the invention described in the present application, and both Declarants are experts in the field of the invention. These experts base their comments on their training, knowledge and experience in the relevant arts, and discuss how the present application provides unexpected and striking results. As discussed in the following, Appellants submit that the opinions of these experts in the fields of cancer research and cancer treatment confirms the non-obviousness of the Appellants' invention.

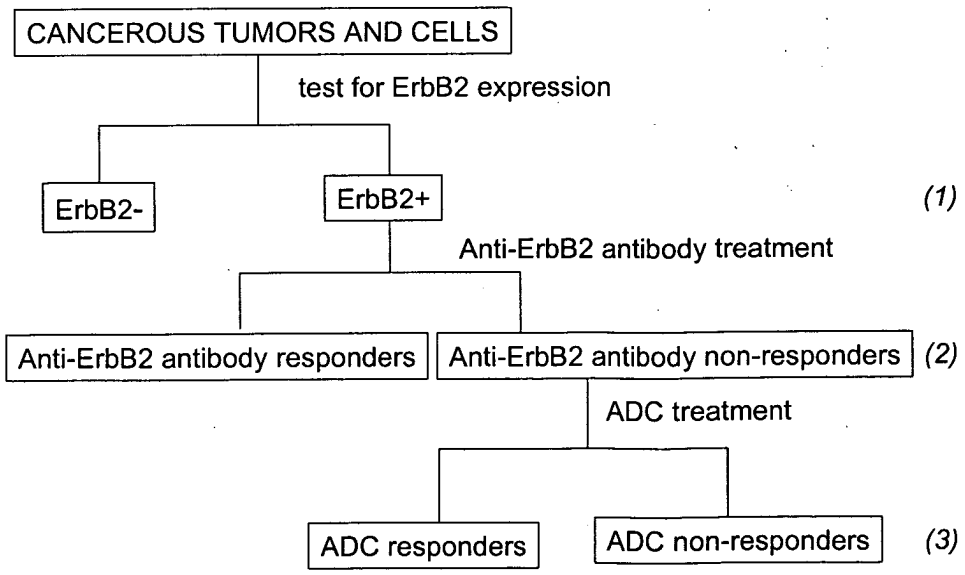
Summary of the Arguments:

The Claimed Invention is Not Obvious under 35 U.S.C. § 103(a) over the Prior Art

The present invention is directed to methods for treating a tumor in a mammal, requiring two steps. The first step comprises identifying a tumor that is characterized by overexpression of an ErbB2 receptor and by not responding, or responding poorly, to treatment with an anti-ErbB2 antibody (where that anti-ErbB2 antibody binds to the 4D5 epitope and has a growth inhibitory effect on SK-BR-3 cells). The second step comprises administering a therapeutically effective amount of a conjugate to the mammal having such a tumor (where the conjugate is a conjugate of a maytansinoid with an anti-ErbB2 antibody which binds to the 4D5 epitope).

Appellants have discovered that it may be useful to determine to which population a patient's tumor belongs when proposing treatment for that patient. Such a discovery is not obvious, as no statement or suggestion in the prior art teaches this element of the claimed invention. In fact, the Examiner indicated that the opposite was believed to be true, as may be seen, for example, from the Examiner's remarks indicating a belief that "almost any population would respond to a maytansinoid conjugate" (Office Action dated March 17, 2005, page 8 line 6). Thus, this element of the claimed method is not obvious over the cited references. Moreover, the art does not teach the conjugates of the treatment step of the claimed methods.

Tumors and tumor cells may be categorized as belonging to different populations based on identifying characteristics. As discussed herein, Appellants have applied this insight and invented novel methods of treating particular tumors based on the characterization of the tumors and their identification as being members of a particular target population for which the claimed methods are directed. As illustrated in the Figure, the broad class of cancerous tumors and cells may be divided into two populations based on the level of expression of ErbB. The population that over-expresses ErbB may be further divided into two different populations on the basis of the response (or lack thereof) to anti-ErbB antibodies (such as HERCEPTIN®). The population that does not respond, or responds only poorly, to anti-ErbB antibodies may be further divided on the basis of response, or lack of response, to antibody-drug conjugates (ADC).



Thus, the broad class of tumors may be divided into several different populations based on a number of different identifying characteristics. Appellants have discovered that some identifying characteristics may be used to provide methods for treating particular tumor populations.

Appellants note that the invention provides a therapeutic method for treating a particular, identified tumor population with a particular treatment. The claimed therapeutic method includes two steps which together form the claimed method. Appellants note that the prior art nowhere recognized or suggested that treatment of the target tumors required the two steps of the present methods.

Moreover, whether or not one believes that "almost any population would respond to a maytansinoid conjugate," determining the population to which a patient belongs provides advantages and benefits not available in the absence of the present methods. For example, identification of a tumor's population allows one to tailor a treatment so as to provide an anti-ErbB2 antibody-maytansinoid conjugate to those patients who require such treatment (those whose tumors do not respond to the antibody alone), while being able to spare those patients whose tumors do respond to the antibody alone the possible added costs and risks (*e.g.,* of toxicity) of the conjugates. Thus, the present methods requiring identification of a tumor's characteristics are not only not obvious, but provide advantages and benefits that are not available without such identification.

Thus, Appellants note that the prior art fails to teach or suggest the claimed invention as a whole. For these reasons at least, whether or not such a population of tumors could have been identified prior to the filing date of the present application, and whether or not an antibody conjugate as required by the present therapeutic methods could have been assembled prior to the filing date of the present application, Appellants submit that the claimed methods are not obvious over the prior art.

Identification of a Problem in the Art

As stated by the Circuit Court of Patent Appeals in *In re Sponnoble*: "[A] patentable invention may be in the discovery of the source of the problem even though the remedy may be obvious once the source of the problem is identified. This part of the 'subject matter as a whole'

which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103." 405 F.2d 578,585, 160 USPQ2d 237,243 (CCPA 1969).

Thus, as recognized by the Circuit Court of Patent Appeals, when considering the invention as a whole it is important to note whether the inventors have identified a problem that was not recognized in the prior art. Appellants submit that they have identified a problem that was not recognized in the prior art, and have provided a solution to that problem.

As discussed above, the claimed invention is a method that includes two steps, to be performed together, and not merely one or the other of the individual steps alone that my have been discussed by the Examiner. Not only does the prior art not teach or suggest the individual steps, but the prior art fails to teach or suggest the claimed methods that combine these steps. The Examiner suggests that the prior art noted that some tumors expressing ErbB2 receptors did not respond to anti-ErbB2 antibodies. However, even if this were true, there is no suggestion in the art to identify such tumors in order to apply treatment methods requiring such anti-ErbB2 antibodies, nor that such methods might be successful or useful.

Where the prior art provides no suggestion or motivation to provide the claimed multi-step therapeutic method, it is also improper to attempt to base an obviousness rejection on a mere suggestion or supposition that the claimed methods might have been "obvious to try." The Federal Circuit has stated that "obvious to try is not the standard" *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 56 USPQ2d 1065 (Fed Cir. 2000) and that "we have consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. §103." *Gillette Co. v. S. C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997).

Appellants submit that the present invention provides novel and unobvious methods for treating tumors identified as overexpressing ErbB2 and also as not responding, or responding poorly, to anti-ErbB2 antibodies which bind to the 4D5 epitope and have a growth inhibitory effect on SK-BR-3 cells. As discussed below, the prior art does not suggest identifying such tumors nor does the prior art suggest providing the antibody conjugates specified in the claims in order to treat tumors that have been so identified. Thus, Appellants submit that the present methods are new, useful, and not obvious.

The Claim Rejections Under 35 U.S.C. §103(a)

One aspect of the rejection deals with the Examiner's apparent failure to accept that the step of identifying the population of tumors to be treated is an effective part of the claimed methods. For example, the Examiner suggests that "the prior art recognizes that there are tumors overexpressing ErbB2 antibody but unresponsive to anti-ErbB2 antibody that has a growth inhibitory effect on SK-BR-3 cell" (page 3, lines 18-20, Office action dated November 2, 2005). However, even if this were the case, knowledge in the art that some tumors do not respond in no way constitutes a suggestion in the art to identify such tumors as part of a therapeutic method for treating that population of tumor that has been identified.

That such "recognition" as suggested by the Examiner does not, in fact, suggest the steps of the present methods may be seen from the Examiner's statement that "extrinsic evidence" is lacking "that a population, even if defined as one that responds poorly or not at all to a specific antibody, such as, for example, trastuzumab, would be a population where it would be unexpected that individuals in the population would not respond to maytansinoid-anti-ErbB2 antibody conjugate" and that "it appears that almost any population would respond to a maytansinoid conjugate" (Office Action, page 8, lines 1-6 of the Office action dated March 17, 2005). The Examiner's statement clearly indicates that it was not obvious to treat such tumors with a method that requires 1) identifying the tumors as recited in the present claims, and then 2) administering the conjugates recited in the claims.

First, Appellants note that the method of Claim 55 requires "an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells" and thus requires active antibodies. It does not include those antibodies that the Examiner characterized as "not capable of causing any inhibition in cell proliferation" (Office Action dated March 17, 2005, page 7, lines 17-18). Thus, it is not the case that most individuals would be expected to respond poorly or not at all to the antibodies recited in the present claims.

Appellants further note that the expert declarations that accompany this Appeal Brief discuss whether it would be unexpected that individuals in the population would not respond to maytansinoid-anti-ErbB2 antibody conjugate. For example, referring to "HERCEPTIN® non-responding patients," Dr. Lutzker notes that the "observation that these patients continue to over-

express HER2 was important and not expected" (page 3, paragraph 12). Dr. Lutzker also stated that "it would not have been obvious to investigate or to determine whether or not a patient fell into that subpopulation of patients" (page 3, paragraph 12). Finally, according to Dr. Lutzker, the information as to whether or not a patient responds poorly, or not at all, to anti-ErbB antibody treatment could be clinically useful (page 3, paragraph 12). Dr. Lutzker said "Thus, it is not clear at this time what characteristics, other than response to HERCEPTIN® alone, distinguish the subpopulations of breast cancer patients" (page 2, paragraph 11).

I. The Existence of the Subpopulation to Which the Claims Are Directed

Appellants have identified a group of tumors that differ from other tumors, including differing from other tumors overexpressing ErbB2 receptors. The Examiner has suggested that it was known that some tumors do not respond to HERCEPTIN® even though they may overexpress ErbB2 (page 5, lines 8-16, Office Action dated November 2, 2005). However, as discussed below, and as noted by the declarants in the accompanying expert declarations, this population of ErbB2-overexpressing tumors differs from other ErbB2-overexpressing tumors not only in its response to anti-ErbB2 antibodies, but also differs in its response to anti-Erb2 antibody-maytansinoid conjugates. Thus, the claimed invention is directed to treating an identifiable population of tumors, and whose response to the claimed treatment with anti-ErbB2 antibody-maytansinoid conjugates is not the same as that of other ErbB2-overexpressing tumors.

The specification provides support for the identification of cells that do not respond, or respond poorly, to anti-ErbB2 antibodies alone; see, for example, Figures 9-14, and the discussion in Example 4 at pages 71-76, which show results regarding tumor cells which do not respond to anti-ErbB2 antibodies alone are shown (*e.g.*, Figure 9).

Thus, the specification provides evidence supporting the response of the population of tumors recited in the claims. Such response provides further evidence that these tumors fall into a different population than other tumors that respond to anti-ErbB2 antibodies alone.

Further evidence in this regard is provided in the attached Declaration of Dr. M. Sliwkowski, a recognized expert on cancer research and one of the inventors of the present application. For example, as discussed by Dr. Sliwkowski (see, for example, paragraphs 10-14 of Dr. Sliwkowski's Declaration) and as disclosed in the figures of the Appendix of Dr.

Sliwkowski's Declaration, cells of the CAlu 3 cell line respond well to treatment with the anti-ErbB2 antibody HERCEPTIN® alone, while cells of the BT474E1 cell line cells respond only poorly to HERCEPTIN® alone.

Thus, substantial evidence is provided in the specification and corroborated by further results attested to by an expert declarant that there are cell lines that do respond well to treatment with an anti-ErbB2 antibody alone, and that there are cell lines that do *not* respond well to treatment with an anti-ErbB2 antibody alone. Accordingly, the population referred to in the claimed invention exists, its existence is supported by substantial evidence, and would be accepted as such by one of ordinary skill in the art.

Furthermore, as discussed by Dr. Stuart Lutzker, a clinical oncologist, in his declaration, such populations are also observed clinically. Dr. Lutzker notes that a recent paper, Spector et al., Jour. of Clin. Onc. 23(11):2502-2512 (2005), discusses the unexpected discovery that HERCEPTIN® non-responding patients continue to express or overexpress ErbB. This paper provides further evidence that some tumors that overexpress ErbB may yet not respond to HERCEPTIN®, as was previously disclosed in the present application and as required by the present claims. Dr. Lutzker states that "[p]rior to this recent observation, it would not have been obvious to investigate or to determine whether or not a patient fell into that subpopulation of patients." Moreover, Dr. Lutzker is of the opinion that such information could be clinically useful, and further stated that "it would be helpful in my clinical practice to have available treatment methods to help those patients whose cancers overexpress ErbB2 yet who do not seem to be helped by anti-ErbB antibody treatment."

II. The Effect of Maytansinoid Conjugates on the Identified Population

Moreover, as discussed by Dr. Sliwkowski and supported by evidence provided by Dr. Sliwkowski in the attached declaration, the different populations of tumors respond differently to anti-ErbB2 antibody-maytansinoid conjugates. Such different response is further evidence of the existence of, and differences between, the populations. In addition, the different responses to treatment with anti-ErbB2 antibody-maytansinoid conjugates makes it critical to determine into which population a tumor falls in determining dosing and treatment for that tumor.

As noted in Dr. Sliwkowski's declaration, CAlu 3 cells respond well to HERCEPTIN® alone; and CAlu 3 cells also respond well to conjugates of HERCEPTIN®-maytansinoid: a conjugate dose of 165 μg/kg DM1 gave a complete response. Inspection of the results provided in Figure 1 of the Sliwkowski declaration indicate that even a lesser dose may have been sufficient for a complete response, as the effect appears to be maximal at that dose.

However, BT474E1 cells respond, if at all, only poorly to HERCEPTIN® alone. The BT474E1 cells do respond to conjugates of HERCEPTIN®-maytansinoid. However, it took a 50% larger dose than required by the CAlu 3 cells (250 μg/kg HERCEPTIN®-DM1) to get a nearly complete response. Note that this response was not a maximal response, so that an even higher dose would be required to achieve the same response as was obtained by 165 μg/kg HERCEPTIN®-DM1 treatment of CAlu-3 cells.

Thus, the population of tumor cells that do not respond or that respond poorly to HERCEPTIN® alone also responds more poorly to HERCEPTIN®-DM1 conjugates than does a cell line that responds well to HERCEPTIN® alone. This difference in response further identifies these groups as being different from each other (*i.e.*, being two different identifiable populations) and identification of these populations has important implications for the successful treatment of tumors from these two groups.

All Steps Must Be Taken Into Account in Determining Non-Obviousness

It is clear from the different responses of these cells, and in particular the different dosages required for complete response to treatment, that determining which population a tumor belongs to (step (i) of the claimed method) may be critical in determining the treatment by anti-ErbB2 antibody-maytansinoid conjugates (step (ii) of the claimed methods). Importantly, the claimed methods include additional steps not suggested in the art.

The Examiner has suggested, after noting that Lewis "suggests using engineered antibody to target therapeutic molecules to tumor cells" (page 6, lines16-17, Office Action dated November 2, 2005) and after noting that Hudziak "contemplated the use of anti-ErbB2 antibodies for the purpose of making immunotoxins" (page 7, lines 2-3, Office Action dated November 2, 2005), that "the prior art recognized that an anti-ErbB2 antibody could be used for the purpose of delivering a cytotoxic moiety to a tumor, especially to tumors that do not respond to the ErbB2

antibody alone even though the tumor overexpresses ErbB2." page 7, lines 3-7). However, the references cited lack any suggestion that any treatment be directed "especially to tumors that do not respond to the ErbB2 antibody alone even though the tumor overexpresses ErbB2." Appellants note that the Examiner did not quote any reference or cite any such suggestion in the summation of the teachings of the cited references provided by the Examiner on pages 6-7 of the Office Action dated November 2, 2005.

In fact, there is no suggestion in the prior art to deliver a cytotoxic moiety "especially to tumors that do not respond to the ErbB2 antibody alone even though the tumor overexpresses ErbB2." Mere evidence in the art that some tumors do not respond to anti-ErbB2 antibodies even though they overexpress ErbB2 in no way constitutes recognition in the art that identifying such a population could have therapeutic benefit, nor that one should treat such identified tumors as claimed in the present methods. As mentioned above, there is no suggestion in the art that the tumor population identified in the present methods should be treated differently than any other tumors, nor is there any suggestion in the art that the tumor population identified in the present methods could be treated differently than any other tumors.

Thus, in contrast to the Examiner's suggestion, the claimed methods provide an effective, and more targeted, method for treating tumors that overexpress ErbB2 receptors that is not suggested in the prior art.

Identifying the population of tumors characterized as required by the claimed invention allows one to treat the tumors selected in the claimed method with the proper effective therapeutic dose of antibody-maytansinoid conjugate. This proper dose differs from that which would be optimal for a tumor cell that does not satisfy the selection criteria required by the claimed invention. Determination of the type of tumor being treated provides information that allows one to provide the treatment appropriate to the cells being treated, and is not a superfluous or irrelevant step.

Appellants note that merely increasing the dose of anti-ErbB2 antibody-maytansinoid conjugates for all patients, in order to avoid determining which population a tumor to be treated belongs to, is not a viable alternative, for at least the reasons that the anti-ErbB2 antibody-maytansinoid conjugates are expected to have toxic side effects that a physician must try to

minimize, and that anti-ErbB2 antibody-maytansinoid conjugates, like all drugs, will have costs associated with them that a patient (or patient's insurance plan), if not the physician, will try to minimize. Thus, the step (i) of determining which population a tumor to be treated belongs to is an effective and integral part of the claimed methods, and must be considered in any determination of the non-obviousness of the claimed invention.

Thus, not only does the prior art fail to suggest determining to which of the populations a tumor belongs, and fail to recognize the usefulness of such a determination, but moreover no reference and no combination of references teaches the claimed method comprising both the above steps. No reference or combination of references suggests, or would motivate one of ordinary skill in the art to perform these steps as claimed. Indeed, this lack of suggestion or motivation is implicitly acknowledged by the Examiner, since if it were true, as suggested by the Examiner (page 8, lines 6-7, Office action dated March 17, 2005), that "it appears that almost any population would respond to a maytansinoid conjugate, because the treatment effect is derived from the toxic action of the maytansinoid on the tumor" then there would be no suggestion or motivation in the art to perform the step (1) above, and no suggestion or motivation to provide the claimed invention comprising all the claimed steps.

The Federal Circuit in *In re Zurko* stated that :

> "[T]o say that the missing step comes from the nature of the problem to be solved begs the question because the Board has failed to show that this problem had been previously identified anywhere in the prior art. *see In re Sponnable* 405 F.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969) ('[A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified.')." *In re Zurko* 42 USPQ2d 1476, 1479 (Fed Cir. 1997) *rehearing en banc granted*, 116 F.3d 874 (Fed. Cir. 1997)

The claimed invention is directed to treating a tumor in a mammal that is characterized by overexpression of an ErbB2 receptor and that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells. The present invention identifies and provides a solution to a problem that was not recognized in the art. No cited art identifies such tumors as targets for treatment, nor do any cited references provide a treatment directed to such tumors.

As indicated by the Examiner's rejections, it was not obvious that identification of the population of tumors to be treated would provide any benefit or would identify tumors treatable by the treatments recited in the claimed methods. Instead, one of ordinary skill in the art might have assumed, either that such antibody-drug conjugates would be ineffective (as discussed above), or, as stated by the Examiner, that " almost any population would respond to a maytansinoid conjugate, because the treatment effect is derived from the toxic action of the maytansinoid on the tumor" and so would find the claimed invention surprising and not obvious.

Failing to identify the such target tumors, and failing to provide any treatments directed to such tumors, no combination of any of the cited references provides the invention as a whole as recited in the pending claims, nor would suggest these claims, nor would provide any reasonable expectation of success for these claims. For example, although the claimed invention requires that a tumor to be treated be identified as a tumor that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells, no reference and no combination of references discusses or suggests this element of the claims. This element is effective, as discussed in the declaration accompanying this paper, at least for the reason that the effective amount of anti-ErbB antibody-maytansinoid conjugate required by such cells is different than the effective amount of anti-ErbB antibody-maytansinoid conjugate required by cells that do respond to anti-ErbB antibody alone.

The pending claims as a whole are directed to inventions which are not found and not suggested in the prior art, and which are not provided by any combination of the cited references. Accordingly, Appellants submit that the claims, when viewed in the light of the above criteria, are not obvious over the cited references.

The Invention as a Whole Need Not Provide the "Best" Alternative

Moreover, "The Federal Circuit stated that a finding that "an invention that is an 'improvement' is not a prerequisite to patentability" since it "is possible for an invention to be less effective than existing devices but nevertheless meet the statutory criteria for patentability." (*Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 1 USPQ2d 1196 (Fed. Cir. 1986))."

As noted above, the Examiner has suggested that "it appears that almost any population would respond to a maytansinoid conjugate, because the treatment effect is derived from the toxic action of the maytansinoid on the tumor" (page 8, lines 6-7, Office action dated March 17, 2005). Appellants note that the present invention provides an effective method for treating a tumor in a mammal, one that requires the identification of a characteristic of a tumor to be treated that is important in determining the treatment of that tumor. Thus, even if the Examiner's suggestion were true, it does not negate the patentability of the present invention.

None of the cited references discusses or suggests, and no combination of the cited references discusses or suggests determining that a tumor does not respond, or responds only poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope. Thus, no combination of the cited references provides or suggests this claim element. Moreover, none of the cited references discuss or suggest, and no combination of the cited references discusses or suggests, a treatment for such a tumor with a conjugate of a maytansinoid with an anti-ErbB2 antibody which binds to the 4D5 epitope. Thus, no combination of the cited references provides or suggests this additional claim element.

Appellants note that evidence in the art that such a non-responding tumor population *might exist* in no way constitutes a suggestion to identify such a tumor population as a step in a method of treating such non-responding tumors. Nor does such evidence provide any motivation to provide such a therapeutic method that requires a step of determining whether a tumor is in that population or not, and then, if it is, to provide the claimed treatment step as a result of such a determination.

As discussed above, the prior art does not suggest, as part of a therapeutic method directed at these particular tumors, that one should determine whether the particular tumors targeted in the present methods respond poorly, or do not respond, to anti-ErbB2 antibodies, and then that one should use the methods of the claims in order to treat that particular tumor population. Accordingly, Appellants submit that regardless of whether or not "almost any population would respond to a maytansinoid conjugate" the present invention provides a non-obvious method for treating a tumor in a mammal.

III. The Maytansinoid Conjugates are not Obvious

Appellants further note that the claimed conjugates and treatment methods are not obvious since one of ordinary skill in the art would not be led to prepare the conjugates of the present claims nor be led to the claimed treatment methods. As noted by Chari in discussing antibody drug conjugates such as antibody-targeted methotrexate, antibody-targeted vinblastine, and antibody-targeted doxorubicin, "in clinical trials conducted so far, early antibody-drug conjugates have failed to live up to the promise of the targeted delivery approach for the treatment of cancer" (page 96, column 1, "Targeted delivery of chemotherapeutics: tumor-activated prodrug therapy," Advanced Drug Delivery Reviews **31**:89-104 (1998)). Thus, the Examiner's statement "it appears that almost any population would respond to a maytansinoid conjugate" (page 8, line 6, Office Action dated March 17, 2005) is not in accordance with the expectations of one of skill in the art at the time of the application.

In addition to the above, and in addition to all prior Amendments (including the amendments mailed on July 30, 2002; February 24, 2003; November 3, 2003 and as corrected on December 10, 2003; June 18, 2004; and November 9, 2004) filed in response to previous Office Actions (the arguments presented therein being hereby incorporated by reference) Appellants present arguments below directed to the specific claim rejections under 35 U.S.C. §103(a) as made or maintained by the Examiner in the present Office Action.

Moreover, the Examiner provided no specific reasons why the combined references cited, or the prior art as a whole, would have provided any motivation to make this invention which includes both these steps. In fact, Appellants submit that the Examiner's comment quoted above is a further indication that the prior art provides *no* motivation to provide the determining step. Motivation to combine the cited references must come from the prior art references themselves, and not as a result of hindsight. *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). "[A] retrospective view of inherency is not substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

Lacking any such discussion or suggestion, the combination of the cited references provides no reasonable expectation of success for the claimed methods. Moreover, as discussed above and in the attached declarations, the present specification reports unexpected results.

Accordingly, since 1), the cited references fail to provide all elements of the claimed invention; since 2), the cited references fail to suggest or to motivate the combination of such elements in an attempt to provide the claimed methods; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable expectation of success were the references to be so combined; since 5) the present invention provides unexpected results; and for other reasons, Appellants respectfully submit that Claims 2, 4-6, 8-21, 24-48, and 55 are not made obvious by the cited references and that the claim rejections under 35 U.S.C. §103(a) are overcome.

Detailed Arguments:

The Claimed Invention is Not Obvious

Appellants submit that the claimed invention is not obvious over the prior art, and is not obvious in view of Chari under the judicially created doctrine of obviousness-type double patenting.

A. The Legal Standard for Obviousness

Obviousness under 35 U.S.C. §103(a) requires several elements, and may not be directed by hindsight based on the disclosure under examination. Thus, the Federal Circuit has stated that:

> "In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure." In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

To reject claims in an application under 35 U.S.C. §103, the PTO bears the initial burden of establishing a *prima facie* case of obviousness (*In re Bell*, 26 U.S.P.Q.2d 1529, 1530 (Fed. Cir. 1993); M.P.E.P. §2142). In order to establish *prima facie* obviousness, three basic criteria must be met.

First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the PTO to arrive at the claimed invention. Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success that the modification or combination suggested by the PTO would succeed (*In re Dow*, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988)). Third, the prior art, either alone or in combination, must teach or suggest ***each and every limitation of the rejected claims*** (emphasis added) (*In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000)). If any one of these criteria are not met, *prima facie* obviousness is not established and Appellants are not required to show new or unanticipated results (*In re Grabiak*, 226 U.S.P.Q. 870 (Fed. Cir. 1985)).

In addition, under 35 U.S.C. §103, each claim must be considered as a whole. As stated by the Federal Circuit in *In re Wright* (838 F.2d 1216, 6 USPQ2d 1959 (Fed. Cir. 1988) "[I]t is the invention as a whole that must be considered in obviousness determinations. The invention as a whole embraces the structure, its properties, and the problem it solves." Similarly, "In determining obviousness, the invention must be considered as a whole without the benefit of hindsight, and the claims must be considered in their entirety." *Rockwell International Corp. v. United States*, 47 USPQ2d 1027, 1031 (Fed. Cir. 1998).

When considering the invention as a whole, it is important to note whether, as here, the inventors have identified a problem that was not recognized in the prior art. As stated by the Circuit Court of Patent Appeals in *In re Sponnoble*: "[A] patentable invention may be in the discovery of the source of the problem even though the remedy may be obvious once the source of the problem is identified. This part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103." 405 F.2d 578,585, 160 USPQ2d 237,243 (CCPA 1969). Similarly, the Federal Circuit in *In re Zurko* stated that :

> "[T]o say that the missing step comes from the nature of the problem to be solved begs the question because the Board has failed to show that this problem had been previously identified anywhere in the prior art. *see In re Sponnable* 405

F.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969) ('[A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified.')." *In re Zurko* 42 USPQ2d 1476, 1479 (Fed Cir. 1997) *rehearing en banc granted*, 116 F.3d 874 (Fed. Cir. 1997).

B. Proper Application of the Legal Standard

The present invention identifies and provides a solution to a problem that was not recognized in the art. The claimed invention is directed to a two-step method of treating a tumor in a mammal, in which the tumor is 1) characterized as being one that overexpresses an ErbB2 receptor and that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells; and then the tumor is 2) treated with a therapeutically effective amount of a conjugate of a maytansinoid conjugated with an anti-ErbB2 antibody which binds to the 4D5 epitope. Thus, the claimed methods are directed to particular tumors, and include a step of identifying those particular tumors as part of the treatment method directed to such tumors.

The Examiner has suggested that the pending claims are made obvious by various cited references, as discussed above. However, as discussed in more detail below, even if combined, the cited references fail to provide all the elements of the claimed invention. No cited art provides or suggests a step of identifying such tumors in particular, nor of identifying such tumors as targets for treatment, nor of providing a treatment that is directed to such tumors, nor do any cited references provide the claimed treatment methods directed to such tumors in particular. Thus, as discussed below, Appellants submit that the claimed invention is not obvious over the cited art.

Issue I: Whether claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41 are patentable under 35 U.S.C. §103(a) over Chari et al., (U.S. Patent 5,208,020; hereafter, Chari) in view of Hudziak (U.S. Patent 5,725,856; hereafter, Hudziak) and further in view of Lewis (Lewis, G.D. et al., J. Immunol., hereafter "Lewis").

Appellants submit that claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41 are patentable over the cited prior art as reciting a method for treating a tumor in a mammal that is not taught and is not suggested by the prior art.

In particular, the claims are directed to methods for treating a tumor in a mammal comprising steps of identifying the tumor as being one that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds the 4D5 epitope and has a growth inhibitory effect on SK-BR-3 cells, and of administering a therapeutically effective amount of a conjugate of an anti-ErbB2 antibody which binds the 4D5 epitope with a maytansinoid. The prior art does not suggest a method including at least these two steps.

In the rejections under Appeal, Chari is presented as providing maytansinoid compounds attached to monoclonal antibodies or their fragments, and as providing methods of killing selected cell populations. Hudziak is presented to provide anti-ErbB2 antibodies and fragments, including growth inhibitory and cytotoxic ant-ErbB2 antibodies. Lewis is presented as discussing tumor cells that overexpress ErbB2 and fail to respond to murine antibody 4D5 by exhibiting growth inhibition.

Chari does not discuss tumors that fail to respond, or respond poorly, to antiErbB2 antibodies, nor does it teach identifying such tumors as part of a treatment regiment directed at such tumors. Chari also fails to teach conjugates comprising anti-ErbB2 antibodies, as noted by the Examiner, and further fails to teach a method of treating a tumor using an anti-ErbB2 antibody conjugated to a maytansinoid (see, e.g., Office Action dated November 2, 2005, page 6, lines 1-7). Hudziak also fails to discuss tumors that fail to respond, or respond poorly, to antiErbB2 antibodies, and fails to discuss identifying such tumors as part of a treatment regiment directed at such tumors. The Examiner noted that Hudziak fails to teach "that the patient has not responded or responded poorly to an unconjugated anti-ErbB2 antibody" (page 5, lines 6-8 of the Office Action dated March 26, 2004). Thus, the combination of these references lack elements of the claimed invention. Appellants respectfully submit that Claims 55, 2, 4, 5, 8-12, 20-33, and 38-41 are not obvious under 35 U.S.C. §103(a) over the cited references.

Appellants respectfully submit that there is no motivation or suggestion in the cited references to combine the cited references in an attempt to provide the claimed invention. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Hudziak and Lewis each fail to disclose and fail to suggest maytansinoid compounds. Thus, there is no link between these references apart from the present disclosure. Although the Examiner suggests that Lewis

"teaches that some tumor cells that overexpress ErbB2 fail to respond to murine antibody 4D5" (page 5, lines 9-10 of the Office Action dated March 26, 2004), Appellants note that Lewis nowhere suggests methods for treating such tumors, and in particular, Lewis nowhere suggests treating such tumors with maytansinoids conjugated to those particular antibodies which Lewis showed did not inhibit the growth of such cells.

In fact, Lewis teaches away from the methods of the present invention. Lewis states that "The sensitivity of breast tumor cell lines to antibody-mediated growth inhibition correlates well with their level of $p185^{HER2}$ overexpression." (page 261, column 2, lines 27-30). Lewis thus teaches that cells that overexpress $p185^{HER2}$ can be treated with anti-ErbB2 antibodies alone. Lewis does not explain the discrepancy between their main conclusion (that antibody-sensitivity increases with increasing $p185^{HER2}$ overexpression) and their observation that some cells fail to respond to anti-ErbB2 antibodies. Lewis further fails to provide any hypothesis or suggestion to explain the existence of such non-responding cells. Moreover, Lewis also fails to suggest a possible treatment for such non-responding cells, and provides no basis for suggesting a possible treatment.

In opposition to the above, the Examiner suggests that "instead Lewis suggest to use engineered antibody to target the therapeutic molecules to tumor cells" (page 8, lines 10-11, Office action dated November 2, 2005). In so doing, the Examiner again asserts that such antibody targeting could be used "especially to tumors that do not respond to the ErbB2 antibody alone even though the tumor overexpresses ErbB2" (page 8, lines 13-14, Office action dated November 2, 2005). However, the Examiner again fails to support the contention that the prior art recognized or suggested that such treatment might be directed "***especially*** to tumors that do not respond to the ErbB2 antibody alone even though the tumor overexpresses ErbB2" (emphasis added). This contention is critical; and, as Appellants have argued and reiterate here, this contention is not supported by the disclosure of the prior art and is incorrect. Contrary to the Examiner's assertion, Lewis, and the prior art as a whole, even if aware of the existence of tumors that overexpress ErbB2 but did not respond to anti-ErbB2 antibodies, fail to suggest directing a treatment to such tumors in particular, and fail to suggest first identifying such tumors as part of a therapeutic method directed at treating such tumors in particular.

Moreover, Chari and Hudziak each also fail to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Accordingly, the cited references either teach away from, or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention.

The cited references fail to provide motivation to be so combined and fail to provide such a suggestion. Thus, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

As stated by the Federal Circuit: "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. ... Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." In re Dembiczak, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999).

As discussed above, the combination of the cited references lacks elements of the claimed invention. Thus, Appellants respectfully submit that, in absence of motivation or suggestion to combine these cited references, and where even the combination of the references lacks elements of the claimed invention, the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

Moreover, the claimed invention provides unexpected results. The target tumors of the present invention are those that do not respond, or respond poorly to anti-ErbB2 antibodies, so that treatments based on these antibodies, on cells shown not to respond to such antibodies, might not be expected to work. Moreover, such cells might be expected to be resistant to other treatments as well. Surprisingly, the present inventors have shown that anti-ErbB2 antibodies

conjugated with maytansinoids are useful in treating tumor cells that do not respond, or respond poorly to anti-ErbB2 antibodies.

The cited references, even if combined, do not provide the claimed invention and fail to suggest or motivate a combination to provide the claimed methods, and provide no reasonable expectation of success for such a combination, since no reference discusses any method of treating the target tumor population. Moreover, as discussed above, the present specification discloses unexpected results. Accordingly, appellants submit that the rejections of Claims 1, 34-37, 42 and 43 under 35 U.S.C. §103(a) are overcome.

Issue II. Whether Claims 55, 2, 4, 5, 8-21, 24-33, 38-41, and 46-48 are patentable under 35 U.S.C. §103(a) over Chari in view of Carter (U.S. Patent 6,054,297, hereafter "Carter") and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above. Carter is presented as providing humanized 4D5 antibodies, and in addition is said by the Examiner to teach each of huMab4D5-1, huMab4D5-2, huMab4D5-3, huMab4D5-4, huMab4D5-5, huMab4D5-6, huMab4D5-7, and huMab4D5-8. Appellants respectfully submit that Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48 are not obvious under 35 U.S.C. §103(a) over the cited references.

As discussed above, neither Chari nor Lewis discuss identifying a population of tumors in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody, nor do either of these references discuss or suggest treating such a population of tumors. In addition, Chari and Lewis provide no motivation or suggestion to be combined to provide the claimed invention. Chari and Lewis are also cited in the present rejections of Claims 1, 2, 4, 5, 8-33, 38-41 and 46-48. Carter is cited in place of Hudziak. However, like Hudziak and Lewis, Carter also lacks disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Thus, the combination of these references not only lacks elements of the claimed invention, but there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

The Examiner suggests that Carter "clearly contemplated the use of immunotoxins in methods of treatment" (page 10, lines 13-14, Office action dated November 2, 2005), and suggests that since Lewis "teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Carter to make the maytansinoid conjugates to the claimed methods" (page 10, lines 16-19, Office action dated November 2, 2005). However, even were this suggestion to be true, the art provides no motivation or suggestion to identify such a population as part of a treatment method, nor to direct a treatment method to that identified population alone.

Carter nowhere contemplates treatments of tumors that overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. In fact, none of the cited references discuss such a population of tumors as a target for treatment; none suggest treatments for such a population of tumors; none of the references suggest treatment of such tumors with maytansinoid conjugates, nor do any of the cited references provide motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population. Lewis does not suggest a treatment for such an identified population, and, in particular, nowhere suggests maytansinoid compounds nor conjugates with such compounds. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

Moreover, neither Chari, Carter nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that have been identified as not responding, or responding poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts. Carter also fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and Carter). Failing to provide such suggestion or motivation, the cited

references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention.

The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. As discussed above, Lewis teaches away from the claimed methods, and Chari and Carter fail to discuss or to suggest the present methods and fail to suggest combining with other references to provide the present methods. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, since 1), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 2), a suggestion that it would have been obvious to try a method similar to the claimed methods does not provide a sufficient basis for a finding of obviousness; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable expectation of success were the references to be so combined; since 5), the present invention provides unexpected results; and for other reasons discussed above, appellants respectfully submit that Chari, in view of Carter and in view of Lewis fail to make Claims 55, 2, 4, 5, 8-33, 38-41 and 46-48 obvious.

Issue III. Whether Claims 55, 2, 4-6, 8-12, 14, 20, 24-33, and 38-41 are patentable under 35 U.S.C. §103(a) over Chari in view of Bacus (U.S. Patent 5,514,554, hereafter "Bacus") and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above. The Examiner stated that "Chari do not teach a method of treating a tumor using an anti-ErbB2 antibody conjugated to maytansinoid" (page 6, lines 1-2). Bacus is presented as providing anti-ErbB2 antibodies that are growth inhibitory, induce cell death, and that induce apoptosis, and that such antibodies may be conjugated to cytotoxic moieties. Appellants respectfully submit that Claims 1, 2, 4-6, 8-12, 14, 20-33, and 38-41 are not obvious under 35 U.S.C. §103(a) over the cited references.

Appellants note that the combination of the cited references lacks elements of the claimed invention.

Although the Examiner suggests that Lewis "teaches that some tumors do not respond to anti-ErbB2 antibodies" (page 12, lines 13-14 of the Office Action dated November 2, 2005), Appellants note that Lewis nowhere suggests identifying a tumor that overexpresses ErbB2 but fails to respond to anti-ErbB2 antibodies in order to treat that population of tumors, nor does Lewis suggest methods particular for treating such tumors. Lewis provides no teaching, no suggestion, and no motivation to determine whether a tumor does not respond, or responds poorly, to anti-ErbB2 antibody and then to provide the conjugate treatment as required by the present claims.

In fact, Lewis teaches away from the methods of the present invention. Lewis states that "The sensitivity of breast tumor cell lines to antibody-mediated growth inhibition correlates well with their level of $p185^{HER2}$ overexpression." (page 261, column 2, lines 27-30). Lewis thus teaches that cells that overexpress $p185^{HER2}$ can be treated with anti-ErbB2 antibodies alone. Lewis does not explain the discrepancy between their main conclusion (that antibody-sensitivity increases with increasing $p185^{HER2}$ overexpression) and their observation that some cells fail to respond to anti-ErbB2 antibodies. Lewis further fails to provide any hypothesis or suggestion to explain the existence of such non-responding cells. Moreover, Lewis also fails to suggest a possible treatment for such non-responding cells, and provides no basis for suggesting a possible treatment.

The Examiner suggests that Bacus "clearly contemplated the use of immunotoxins in methods of treatment" (page 12, lines 10-11, Office action dated November 2, 2005), and suggests that since Lewis "teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Bacus to make the maytansinoid conjugates to the claimed methods" (page 12, lines 13-15, Office action dated November 2, 2005). However, even were this suggestion to be true, the art provides no motivation or suggestion to identify such a population as part of a treatment method, nor to direct a treatment method to that identified population alone.

There is no motivation or suggestion in the cited references to combine the cited references in an attempt to provide the claimed invention. Like Lewis, Bacus also lacks disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure or suggestion of identifying a tumor population that overexpresses ErbB2 but does not respond, or responds poorly, to anti-ErbB2 antibodies. Chari lacks any disclosure or suggestion of anti-ErbB2 antibodies, and, as noted by the Examiner, Chari fails to teach conjugates comprising anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

The combination of these references fails to suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment directed to such tumors. Lewis actually teaches away from such concepts. Bacus also fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Accordingly, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and Bacus). Failing to provide such suggestion or motivation, the combined references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention. Appellants respectfully submit that Claims 1, 2, 4, 5, 8-12, 20-33, and 38-41 are not obvious under 35 U.S.C. §103(a) over the cited references.

The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Appellants respectfully submit that, in absence of motivation or suggestion to combine these cited references, lacking any teaching or suggestion of elements of the claimed invention, and failing to provide an expectation of success were such elements to be combined,

Appellants submit that the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails and respectfully submit that Chari, in view of Bacus and in view of Lewis fail to make Claims 55, 2, 4-6, 8-12, 14, 20-33 and 38-41 obvious.

Issue IV. Whether Claims 55, 2, 8-14, 20, and 24-33 are patentable under 35 U.S.C. §103(a) over Chari in view of Huston et al. (U.S. Patent 5,877,305, hereafter "Huston") and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above, the Examiner stating that "Neither Chari nor Lewis teaches conjugates comprising an anti-ErbB2 antibody (or anti-ErbB2 antibody fragments) and neither Chari nor Lewis teach methods for treatment of metastatic breast cancer." (page 9, lines 13-15, Office Action dated March 26, 2004). Huston is presented as providing single-chain Fv that bind to ErbB2, and methods of treating cancer comprising linking the Fv to an agent that can limit tumor proliferation, and methods for treating metastatic breast cancer (page 9, lines 17-21). Appellants respectfully submit that Claims 1, 2, 8-14, and 20-33 are not obvious under 35 U.S.C. §103(a) over Chari, Lewis and Huston.

Appellants note that the combination of the cited references lacks elements of the claimed invention.

No cited reference discusses or suggests identifying tumors which overexpress ErbB2 but fail to respond to anti-ErbB2 antibodies. Lewis and Huston each lack disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

The Examiner suggests that Huston "clearly contemplated the use of single-chain Fv linked to a therapeutic agent in methods of treatment" (page 14, lines 6-7, Office action dated November 2, 2005), and suggests that since Lewis "teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of Huston to make the maytansinoid conjugates to the claimed methods" (page 12, lines 10-12, Office action dated November 2, 2005). However, even were this suggestion to be true, the art provides no

motivation or suggestion to identify such a tumor population as part of a treatment method, nor to direct a treatment method to that identified population alone.

Huston fails to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. As discussed above, neither Chari nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts, as discussed above. Accordingly, the cited references either teach away from, or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and Huston).

There is no motivation or suggestion in the cited references to combine the cited references in an attempt to provide the claimed invention. Like Lewis, Huston also lacks disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure or suggestion of identifying a tumor population that overexpresses ErbB2 but does not respond, or responds poorly, to anti-ErbB2 antibodies. Chari lacks any disclosure or suggestion of anti-ErbB2 antibodies, and, as noted by the Examiner, Chari fails to teach conjugates comprising anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention. The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Appellants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

Huston, which does not mention maytansinoid compounds, nowhere contemplates treatments with maytansinoid-antiErbB2 antibody conjugates, and provides no suggestion of such treatments. Huston also fails to discuss or even suggest treatments of tumors that overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. In fact, none of the cited references discuss determining whether a tumor does not respond, or responds poorly, to anti-ErbB2 antibody treatment as part of a method for treating those having such tumors; none discuss such a population of tumors as a target for treatment; none suggest treatments for such a population of tumors; none of the references suggest treatment of such tumors with maytansinoid conjugates, nor do any of the cited references provide motivation or suggestion to combine with the other references to treat such a population, or to provide such treatment to such a population. Lewis fails to suggest a treatment for such cells, and, in particular, nowhere suggests maytansinoid compounds nor conjugates with such compounds. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. As discussed above, Lewis teaches away from the claimed methods, and Chari and Huston fail to discuss, or suggest, the present methods or to suggest combining with other references to provide the present methods. Thus, as discussed above, the combined references lack elements of the claimed invention, the references provide no motivation or suggestion to be combined to provide the claimed invention, and provide no reasonable expectation of success for such a combination. Moreover, as discussed above, the present specification reports unexpected results. Accordingly, appellants respectfully submit that Chari, in view of Huston and in view of Lewis fail to make Claims 1, 2, 8-14, and 20-33 obvious.

Issue V. Whether Claims 55, 2, 8-12, 24-33, and 38-41 are patentable under 35 U.S.C. §103(a) over Chari in view of King (U.S. Patent 5,747,261, hereafter "King") and further in view of Lewis.

Claims 1, 2, 8-12, 24-33, and 38-41 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of King and further in view of Lewis.

Chari and Lewis are presented by the Examiner as discussed above. King is presented as providing methods for treating cancer that express high levels of ErbB2, using antibodies to ErbB2 linked to agents that are toxic to cells (page 11, lines 1-4). Appellants respectfully submit that Claims 1, 2, 8-12, 22-33 and 38-41 are not obvious under 35 U.S.C. §103(a) over Chari, Lewis and King.

Lewis and King each lack disclosure of maytansinoids, antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari lacks any disclosure of, and lacks any suggestion of, anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

The Examiner notes that the rejections are based on a combination of references, and suggests that King "teaches methods for treating cancer that express high levels of ErbB2" (page 15, lines 16-17, Office action dated November 2, 2005) and that King "clearly contemplated the use of an antibody linked to one or more agents that will cause injury to cells in methods of treatment" (page 16, lines 4-6, Office action dated November 2, 2005), and suggests that since Lewis "teaches that some tumors do not respond to anti-ErbB2 antibodies, one would have been motivated to use the antibodies of King to make the maytansinoid conjugates to the claimed methods" (page 16, lines 8-11, Office action dated November 2, 2005). However, even were this suggestion to be true, the art provides no motivation or suggestion to identify such a tumor population as part of a treatment method, nor to direct a treatment method to that identified population alone.

King fails to disclose or to suggest any methods directed in particular to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. As discussed above, neither Chari nor Lewis suggest any methods for treating ErbB2 overexpressing tumors that do not respond, or respond poorly to, anti-ErbB2 antibodies, and provide no basis for suggesting a possible treatment. Lewis actually teaches away from such concepts. Accordingly, the combination of these references lacks elements of the claimed invention. In addition, the cited references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the

claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody (Chari and King). Failing to provide such suggestion or motivation, the cited references fail to suggest or motivate the combination of those references in an attempt to provide the claimed invention. The cited references failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness.

Thus, Appellants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails.

The Examiner states that "In view of the teachings of Lewis, it would not have been surprising that there exists a population of patients that despite overexpression of ErbB2, would respond poorly to an anti-ErbB2 antibody that was not conjugated to a maytansinoid." (page 7, lines 6-9 of the Office Action dated November 2, 2005, emphasis added). Appellants note that the question of whether or not *it would have been surprising that such a population of patient exists* is not that the proper standard for presenting a case for obviousness, "obvious to try" not being equated with obviousness under 35 U.S.C. §103. The Federal Circuit has stated that "we have consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. §103." *Gillette Co. v. S. C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1997).

Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. As discussed above, Lewis teaches away from the claimed methods, and Chari and King fail to discuss, or suggest, the present methods or to suggest combining with other references to provide the present methods. Moreover, as discussed above, the present specification reports unexpected results. Accordingly, since 1), the combined references lack elements of the claimed invention, 2), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 3), a suggestion that it would have been obvious to try a method similar

to the claimed methods does not provide a sufficient basis for a finding of obviousness; since 4), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 5), the cited references provide no reasonable expectation of success were the references to be so combined; since 6), the present invention provides unexpected results; and for other reasons discussed above, appellants respectfully submit that Chari, in view of King and in view of Lewis fail to make Claims 55, 2, 8-12, 22-33, and 38-41 obvious.

Issue VI. Whether Claims 55, 34, 44, and 45 are patentable under 35 U.S.C. §103(a) over Chari in combination with Hudziak, Bacus, Huston or King in view of Lewis and further in view of Senger (U.S. Patent 6,022,541, hereafter "Senger").

Hudziak is presented by the Examiner to provide anti-ErbB2 antibodies and fragments, including growth inhibitory and cytotoxic ant-ErbB2 antibodies. As mentioned above, the Examiner acknowledges that Hudziak fails to teach "that the patient has not responded or responded poorly to an unconjugated anti-ErbB2 antibody" (page 5, lines 6-8 of the Office Action dated March 26, 2004).

Lewis is presented by the Examiner as discussing tumor cells that overexpress ErbB2 and fail to respond to murine antibody 4D5 by exhibiting growth inhibition.

Chari, Hudziak, Huston, King and Lewis are presented by the Examiner as discussed above. The Examiner characterizes Claims 1, 34,44 and 45 as drawn to treatment methods comprising administration of a maytansinoid conjugated to an antibody that binds ErbB2, and a second antibody that may be conjugated to any cytotoxic agent (page 12, lines 3-6). The Examiner states that Chari with Hudziak or Bacus or Huston or King fail to teach methods using combinations of at least two antibodies.

Senger is presented to discuss treatment of tumors using at least two antibodies that bind to vascular permeability factor (VPF) and which may be conjugated to a toxin (page 12, lines 11-14), and as providing an "example of a treatment strategy where an antigen is targeted with two different antibodies, where each are conjugated to a toxin" (page 18, lines 1-2, Office Action dated November 2, 2005).

However, except for Chari, all the cited references lack disclosure of maytansinoids, or of antibody conjugates including maytansinoids, or any suggestion of such compounds or of their possible uses. Chari and Senger lack any disclosure or suggestion of anti-ErbB2 antibodies. No relation between VPF and ErbB2 or between VPF antibodies and maytansinoids is suggested. Although the Examiner presents Senger as providing an example of a treatment strategy where an antigen is targeted with two different antibodies, where each antibody is conjugated with a toxin, there is no link apparent, and the Examiner provides no explanation for a link, between VPF and tumors which overexpress ErbB2 yet do not respond, or respond poorly, to anti-ErbB2 antibodies. Thus, there is no link between these references apart from the present disclosure, and no suggestion or motivation to combine the references in an attempt to provide the present invention.

Although the Examiner notes that "the rejection is based on a combination of references" (page 17, lines 8-9, Office Action dated November 2, 2005), Appellants note, as discussed above, that even when combined, the cited references lack elements of the claimed invention and fail to make obvious the claimed methods requiring two steps directed at a particular, identified tumor population.

The cited references also fail to disclose or to suggest any methods directed to treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. As discussed above, Lewis actually teaches away from such treatments. Accordingly, the combination of the cited references lacks elements of the claimed invention, and the references either teach away from (Lewis, as discussed above), or provide no positive suggestion or motivation to provide the claimed methods for treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody.

The Examiner suggests that "because Senger provides an example of a treatment strategy where an antigen is targeted with two different antibodies, where each are conjugated to a toxin" (page 12, line 21 to page 13, lines 1-2), it would have been obvious to combine Chari with either of Bacus, Huston or King in view of Lewis. However, none of these references suggests or motivates such a combination, the references fail to teach a relationship between anti-VPF

antibodies, treatments with such antibodies, and the present methods, and none of the cited references suggests or motivates methods of treating a tumor in a mammal that overexpresses ErbB2 and that also does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Thus, the cited references fail to provide any motivation to combine in an attempt to provide the present invention.

Failing to provide motivation to be so combined and failing to suggest such a combination, such a combination must be impermissibly motivated by hindsight. However, hindsight is not a proper basis for combining references in an attempt to present a case for obviousness. Failing to provide suggestion or motivation to be combined, the cited references also fail to provide a reasonable expectation of success for such a combination. Thus, Appellants respectfully submit that, in absence of motivation or suggestion to combine these cited references, at least that element of the *prima facie* case for obviousness under 35 U.S.C. §103(a) fails. Moreover, as discussed above, the present specification reports unexpected results.

Accordingly, since 1) the combination of the cited references lacks elements of the claimed invention, since 2), the cited references fail to suggest or to motivate the combination in an attempt to provide the claimed methods; since 3), a suggestion for combining the references arises not out of the references but appears to be based on impermissible hindsight; since 4), the cited references provide no reasonable expectation of success were the references to be so combined; since 5), the present invention provides unexpected results; and for other reasons discussed above, Appellants respectfully submit that the rejections of Claims 55, 34, 44 and 45 under 35 U.S.C. §103(a) are overcome.

Issue VII. Whether Claims 55, 34-37, 42, and 43 are patentable under 35 U.S.C. §103(a) over Chari in combination with Hudziak, Bacus, Huston or King in view of Lewis and further in view of Sliwkowski et al. (J. Biol. Chem. 269:14661-14665 (1994), hereafter "Sliwkowski") or Carter. Claims 55, 34-37, 42, and 43 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chari in view of Hudziak in view of Lewis, and further in view of Sliwkowski or Carter.

Chari, Hudziak, Bacus, Huston, King and Lewis have been discussed above, and it has been noted that the combination of these references lacks elements of the claimed invention,

including lacking discussion or suggestion of identifying a tumor that overexpresses ErbB2 and that does not respond, or responds poorly, to anti-ErbB2 antibodies, and as lacking discussion or suggestion of treatment directed at such identified tumors.

Sliwkowski is presented as discussing an anti-ErbB2 antibody, 2C4, that "may be used to inhibit the binding of heregulin (a growth factor) to ErbB3" (page 18, lines 18-19, Office action dated November 2, 2005) and Carter is presented as discussing that "huMab4D5-8 acts to recruit immune effector cells to a tumor" (page 18, lines 19-20, Office Action dated November 2, 2005). The Examiner suggests that it would be obvious to rely on these references for the use of a second antibody to block the effects of a growth factor or to recruit immune effector cells to a tumor.

However, none of the references, including neither Sliwkowski nor Carter, discuss treatment of a tumor in a mammal where that tumor has been determined to overexpress ErbB2 and also not to respond, or to respond poorly, to treatment with an anti-ErbB2 antibody. The combined references do not suggest a step of making such a determination as part of a multi-step treatment method directed at such a tumor population in particular. In addition, as discussed above, the conjugates of the claimed methods are not taught by the prior art; nor are they suggested by the prior art; nor does any reference or combination of references suggest the purpose of the methods of the present claims..

Moreover, the present disclosure provides unexpected results. The target tumors of the present invention are those that do not respond, or respond poorly to anti-ErbB2 antibodies, so that treatments based on these antibodies would not be expected to work. Surprisingly, the present inventors have shown that anti-ErbB2 antibodies conjugated with maytansinoids are useful in treating tumor cells that do not respond, or respond poorly to anti-ErbB2 antibodies. As discussed in *in re Kerkhoven*, it appears that one may refute an allegation of obviousness where inventors show superiority over the cited references (see, *e.g.*, page 1973, column 1, lines 3-10, discussing Kerkhoven's failure to do so). Thus, for this reason as well, Appellants submit that Claims 1, 34-37, 42 and 43 are not obvious over the cited references.

The cited references thus fail to suggest or motivate a combination to provide the claimed methods, and provide no reasonable expectation of success for such a combination, since no

reference discusses any method of first identifying, and then second, treating the target tumor population. Moreover, as discussed above, the present specification discloses unexpected results.

Accordingly, appellants submit that the rejections of Claims 55, 34-37, 42 and 43 under 35 U.S.C. §103(a) are overcome.

Issue VIII. Whether Claims 55, 4-6, 8-19, 24, 25, 27, and 32 are patentable under 35 U.S.C. §103(a) over Iwassa (U.S. Patent 5,217,713, hereafter "Iwassa") in combination with Carter, Hudziak, Bacus, Huston, or King, in view of Lewis.

Carter, Hudziak, Bacus, Huston, King and Lewis are presented by the Examiner as discussed above. Iwassa is presented as providing an immunocomplex that comprises a bispecific antibody that binds to a tumor antigen and to a maytansinoid.

The Examiner suggests that the motivation to combine the references is derived from the discussion of Iwassa that it may be desirable to increase the "selectivity of maytansinoid constructs and any of Carter, Hudziak, Baccus [sic], Huston or King teaches that anti-ErbB2 antibodies are useful as carriers to increase selectivity of toxins" (page 20, lines 8-10, Office action dated November 2, 2005). The Examiner previously noted that Iwassa "fails to teach that the immunocomplex binds to the ErbB2 tumor antigen" (page 15, lines 5-6 of the Office Action dated March 25, 2004). Appellants note that Iwassa also fails to suggest identifying or targeting tumors that overexpress the ErbB2 tumor antigen and also fail to respond, or only respond poorly, to anti-ErbB2 antibodies.

However, as discussed above, the combined references fail to provide methods requiring first identifying whether a tumor overexpresses ErbB2 and does not respond, or responds poorly, to anti-ErbB2 antibodies, and then treating such identified tumors with conjugates of anti-ErbB2 antibodies with a maytansinoid.

Carter, Hudziak, Bacus, Huston and King have been discussed above, and it has been noted that the combination of these references lacks elements of the claimed invention. Moreover, as discussed above, there is no motivation or suggestion to combine them in an attempt to provide the claimed invention including these missing elements.

Thus, there being no suggestion to combine the cited references in those references themselves, such a suggestion must come from the present disclosure, and so be based on

impermissible hindsight, or arise out of a belief that it might have been obvious to try such a combination. However, as discussed above, "obvious to try" may not be equated with obviousness under 35 U.S.C. §103. Accordingly, Appellants respectfully submit that the rejections of Claims 55, 4-6, 8-19, 22-25, 27 and 32 under 35 U.S.C. §103(a) are overcome.

The Claimed Invention is Not Obvious under the Judicially Created Doctrine of Obviousness-type Double Patenting

Issue IX. Whether Claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41 are patentable under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-18 of Chari in view of Hudziak and further in view of Lewis.

A. The Legal Standard for Obviousness-type Double Patenting

Obviousness-type double patenting is a judicially created doctrine grounded in public policy with the primary intent to prevent prolongation of the patent term by prohibiting claims in a second patent that are not patentably distinct from the claims in a first patent. "The fundamental reason for the rule [of obviousness-type double patenting] is to prevent unjustified timewise extension of the right to exclude granted by a patent no matter how the extension is brought about." In re Van Ornum, 686 F.2d 937, 943-44, 214 USPQ 761, 766 (CCPA 1982) (quoting In re Schneller, 397 F.2d 350, 158 USPQ 210, 214 (CCPA 1968)). See also Eli Lilly & Co, v. Barr Labs, Inc. 58 USPQ2d 1865, 1877 (Fed. Cir. 2001), discussing the limited duration of the patent term: "The judicially-created doctrine of obviousness-type double patenting cements that legislative limitation by prohibiting a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent. In re Longi, 759 F.2d 887, 892, 225 USPQ 645, 648 (Fed. Cir. 1985) (explaining that, even though no explicit statutory basis exists for obviousness-type double patenting, the doctrine is necessary to prevent a patent term extension through claims in a second patent that are not patentably distinct from those in the first patent).

As discussed in Lilly v. Barr (58 USPQ2d 1865, 1878 (Fed. Cir. 2001)), "a later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting. In re Berg, 140 F.3d 1428, 1431, 46 USPQ2d 1226, 1229 (Fed.

Cir. 1998). A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim. In re Longi, 759 F.2d at 896, 225 USPQ at 651 (affirming a holding of obviousness-type double patenting because the claims at issue were obvious over claims in four prior art patents); In re Berg, 140 F.3d at 1437, 46 USPQ2d at 1233 (Fed. Cir. 1998) (affirming a holding of obviousness-type double patenting where a patent application claim to a genus is anticipated by a patent claim to a species within that genus)."

As stated in the MPEP at 804, "Since the rejection is based on obviousness-type *double patenting*, one should look to the inventions claimed in the two applications. Anything that is disclosed but not claimed is irrelevant."

B. Proper Application of the Legal Standard for Obviousness-type Double Patenting

There is a common inventor between the present application and between Chari (Walter Blattler). For this reason, the above "double-patenting" rejection has been issued. However, even having a common inventor does not make the claimed invention obvious over the cited art. As discussed above, Chari fails to discuss or suggest determining whether a tumor does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells. Chari does not discuss an anti-ErbB2 antibody which has a growth inhibitory effect on SK-BR-3 cells, nor does Chari discuss identifying a tumor that overexpresses ErbB2 and does not respond, or responds poorly, to anti-ErbB2 antibodies. With respect to the allegation of *double patenting*, Appellants note that Chari does not claim a method for treating a tumor identified as being characterized by overexpression of an ErbB2 receptor, nor as being a tumor that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells. Chari does not claim a method including a step of administering a therapeutically effective amount of a conjugate of an anti-ErbB2 antibody which binds to the 4D5 epitope with a maytansinoid to a mammal having such a tumor.

Hudziak and Lewis fail to provide these missing teachings. As discussed above, neither Hudziak nor Lewis, nor the combination of the two, nor the combination of all three cited references, provide a step of identifying a tumor as being characterized by overexpression of an

ErbB2 receptor and as being a tumor that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells. No reference, nor combination of the cited references, provides a step of administering a therapeutically effective amount of a conjugate of an anti-ErbB2 antibody which binds to the 4D5 epitope with a maytansinoid to a mammal having such a tumor.

Accordingly, the combination of the cited references failing to provide the elements of the claimed invention, providing no suggestion or motivation to combine to so provide these elements, and failing to provide any reasonable expectation of success if such a combination were made, Appellants submit that the cited references fail to make claims 55, 2, 4, 5, 8-12, 14-17, 20, 21, 24-33, and 38-41 obvious under the judicially created doctrine of obviousness-type double patenting.

CONCLUSION

For the reasons given above, Appellants respectfully submit that the present specification clearly discloses an invention that is not obvious over the prior art. Accordingly, Appellants respectfully request withdrawal of all outstanding rejections of Claims 2, 4-6, 8-21, 24-48 and 55.

Please charge any fees, including fees for extension of time or other fees, or credit any overpayment to Deposit Account No. **08-1641** referencing Attorney's Docket No.: **39766-0073 A2**.

Respectfully submitted,
HELLER EHRMAN LLP

Date: February 23, 2006

By: _____
James A. Fox (Reg. No. 38,455)

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8. CLAIMS APPENDIX

Claims on Appeal

1. (canceled)

2. The method of claim 55 wherein the mammal is human.

3. (canceled)

4. The method of claim 55 wherein the anti-ErbB2 antibody is a growth inhibitory antibody effective to inhibit the growth of SK-BR-3 breast tumor cells *in vitro*.

5. The method of claim 55 wherein the anti-ErbB2 antibody induces cell death when applied at an effective concentration *in vitro* to SK-BR-3 cells.

6. The method of claim 55 wherein the anti-ErbB2 antibody induces apoptosis when applied at an effective concentration *in vitro* to SK-BR-3 cells.

7. (canceled)

8. The method of claim 55 wherein the tumor is cancer.

9. The method of claim 8 wherein the cancer is selected from the group consisting of breast, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon, colorectal, thyroid, pancreatic, prostate and bladder cancer.

10. The method of claim 9 wherein the cancer is breast cancer.

11. The method of claim 10 wherein the breast cancer overexpresses ErbB2 at a 2+ level or more.

12. The method of claim 11 wherein the breast cancer overexpresses ErbB2 at a 3+ level.

13. The method of claim 12 wherein the breast cancer is a metastatic breast cancer.

14. The method of claim 12 wherein the antibody has a biological characteristic of a 4D5 monoclonal antibody (ATCC CRL 10463) such that the antibody shows a growth inhibitory effect on SK-BR-3 cells in a manner that is dependent on the ErbB2 expression level and/or blocks binding of monoclonal antibody 4D5 to ErbB2.

15. The method of claim 14 wherein the antibody binds essentially the same epitope as a 4D5 monoclonal antibody (ATCC CRL 10463).

16. The method of claim 14 wherein the antibody is the monoclonal antibody 4D5 (ATCC CRL 10463).

17. The method of claim 14 wherein the antibody is humanized.

18. The method of claim 17 wherein the antibody is selected from the group consisting of humanized antibodies huMAb4D5-3, huMAb4D5-4, huMAb4D5-5, huMAb4D5-6, huMAb4D5-7 and huMAb4D5-8.

19. The method of claim 18 wherein the antibody is humanized antibody huMAb4D5-8.

20. The method of claim 55 wherein the antibody is an antibody fragment.

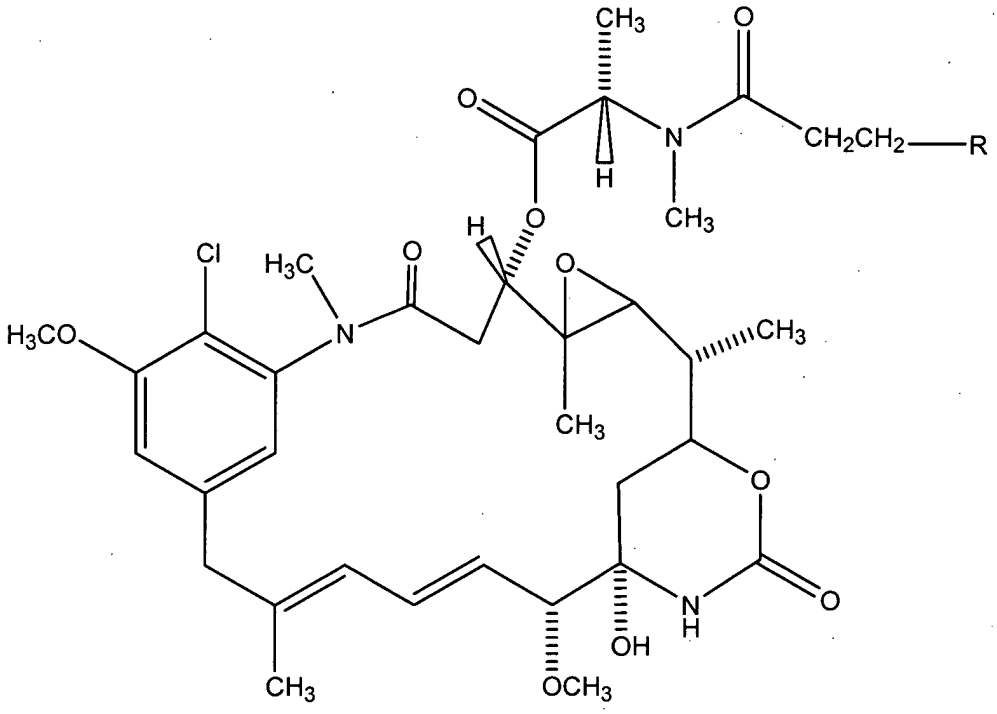
21. The method of claim 20 wherein the antibody fragment is selected from the group consisting of a Fab, Fab', $F(ab')_2$, F_v fragment, diabody, linear antibody, and single-chain antibody molecule.

22-23. (canceled)

24. The method of claim 55 wherein the maytansinoid is a maytansinol ester.

25. The method of claim 24 wherein the maytansinoid is a C-3 ester of maytansinol.

26. The method of claim 25 wherein the maytansinoid is DM1 having the structure



wherein R is SH.

27. The method of claim 55 wherein the antibody and maytansinoid are conjugated by a bispecific chemical linker.

28. The method of claim 27 wherein said chemical linker is N-succinimidyl-4(2-pyridylthio)propanoate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) or N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP).

29. The method of claim 55 wherein the antibody and maytansinoid are conjugated by a linking group selected from the group consisting of a disulfide, thioether, acid labile, photolabile, peptidase labile, and esterase labile group.

30. The method of claim 29 wherein the linking group is a disulfide or a thioether group.

31. The method of claim 30 wherein the linking group comprises a disulfide group.

32. The method of claim 55 wherein the conjugate comprises 1 to about 10 maytansinoid molecules per antibody molecule.

33. The method of claim 32 wherein the conjugate comprises from about 3 to about 5 maytansinoid molecules per antibody molecule.

34. The method of claim 55 further comprising the administration of a second antibody which binds ErbB2.

35. The method of claim 34 wherein the second antibody comprises monoclonal antibody 2C4 or humanized 2C4.

36. The method of claim 34 wherein the second antibody is humanized antibody, huMAb4D5-8.

37. The method of claim 55 wherein treatment with the conjugate is followed by treatment with an unconjugated anti-ErbB antibody.

38. The method of claim 32 wherein the conjugate is administered weekly at a dose of 0.1 to 10 mg/kg body weight.

39. The method of claim 38 wherein said administration is followed by a dose of 0.3 mg/kg body weight approximately 10 weeks later.

40. The method of claim 33 wherein the conjugate is administered weekly at a dose of 1 to 3 mg/kg body weight.

41. The method of claim 40 wherein said administration is followed by a dose of 0.3 mg/kg body weight approximately 10 weeks later.

42. The method of claim 55 wherein the conjugate is administered weekly at a dose of 0.1 to 5 mg/kg body weight for 4 to 6 weeks, followed by maintenance treatment with unconjugated anti-ErbB2 antibody.

43. The method of claim 42 wherein the unconjugated antibody is humanized antibody huMAb4D5-8 or humanized 2C4.

44. The method of claim 34 wherein said second antibody is conjugated with a cytotoxic agent.

45. The method of claim 44 wherein the cytotoxic agent is a maytansinoid.

46. The method of claim 55 wherein said treatment has an improved objective response rate compared to treatment with huMAb4D5-8 alone.

47. The method of claim 55 wherein said treatment has a longer duration of response than treatment with huMAb4D5-8 alone.

48. The method of claim 55 wherein said treatment results in increased survival of the mammal treated compared with treatment with huMAb4D5-8 alone.

49-54. (canceled)

55. A method for the treatment of a tumor in a mammal, comprising the steps of (i) identifying said tumor as being characterized by overexpression of an ErbB2 receptor and as being a tumor that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody which binds to the 4D5 epitope and which has a growth inhibitory effect on SK-BR-3 cells, and (ii) administering to a mammal having said tumor a therapeutically effective amount of a conjugate of an anti-ErbB2 antibody which binds to the 4D5 epitope with a maytansinoid.

9. EVIDENCE APPENDIX

1. Declaration of Stuart Lutzker, M.D. under 35 C.F.R. §1.132

2. Declaration of Mark Sliwkowski, Ph.D. under 35 C.F.R §1.132

Items 1-2 were submitted with Appellants' Response filed September 8, 2005, and considered and discussed by the Examiner in the Final Office Action mailed November 2, 2005.

10. ADDITIONAL INFORMATION

None.

Re: United States Patent Application No. 09/811,123
Filed: March 16, 2001
Title: Methods of Treatment Using Anti-ErbB Antibody-Maytansinoid Conjugates
Inventors: ERICKSON et al.

DECLARATION

I, Stuart Lutzker of Walnut Creek, California, do declare that:

1. I am a medical doctor with experience treating cancer patients, including breast cancer patients.

2. I have over 14 years of experience in medical oncology research and clinical oncology. I received M.D. and Ph.D. degrees from Columbia University, New York. My medical training includes an internship and residency in internal medicine at Yale University, and a medical oncology fellowship at Yale University and Robert Wood Johnson Medical School/University of Medicine and Dentistry of New Jersey.

3. I am currently employed as Associate Medical Director at Genentech, Inc. I have previously served as an Assistant Professor of Medicine at Robert Wood Johnson Medical School/University of Medicine and Dentistry of New Jersey. As the lead medical director of the HER2 drug conjugate team at Genentech, I was responsible for planning, gathering and co-coordinating the scientific work related to development and the clinical plan for HER2 drug conjugate therapeutic candidates. I am an author on over twenty published scientific and clinical articles related to my work, have published many abstracts and presented my work at numerous scientific and medical meetings.

4. I have worked with other clinicians who are engaged in treating patients in these and in related clinical areas and have observed their level of skill. Based on my education, training, and extensive experience as a medical doctor treating cancer patients, I have direct knowledge of the skills and knowledge of one of ordinary skill in the art in the fields related to antibody treatments for cancer, and to antibody-toxin conjugate treatments for cancer.

5. It is my considered opinion, based on my experience as a clinician, that the level of skill in the relevant art is very high, most medical doctors in the area of cancer treatment having advanced medical training including residency and often fellowship training and experience.

6. I have read and am familiar with the specification and pending claims of the present application. Based on my training and experience, I am familiar with scientific fields related to antibody treatments for cancer, and to antibody-drug conjugates.

7. Based on my clinical experience and knowledge, I believe that about 18-25% of breast cancer patients overexpress ErbB2 (depending on the method testing).

8. The anti-ErbB2 antibody HERCEPTIN® is indicated for patients with breast cancer that over-express HER2 or have evidence of HER2 gene amplification.

9. The clinical benefit of HERCEPTIN® treatment varies based upon the clinical setting and whether it is given as a single agent or in combination with chemotherapy. Response rates to treatment with HERCEPTIN® alone vary from 15 to 26%. HERCEPTIN® is also used in combination with other cancer treatments.

10. Analysis of randomized clinical trial data in HER2+ MBC (metastatic breast cancer) indicates that HERCEPTIN® provides improved response rate, time to progression and survival when combined with chemotherapy. In the pivotal study of HERCEPTIN® with chemotherapy (either an anthracycline or paclitaxel), the response rate increased from 32 to 50%; many patients with prolonged stable disease also benefited from HERCEPTIN® in this trial so the exact percentage of patients with benefit cannot be calculated. In a single agent study of HERCEPTIN®, 38% of patients had clinical benefit defined as either a response or stable disease for 6 months. The remaining patients gained either no or little clinical benefit from single agent HERCEPTIN® as described in U.S. Patent application 09/811,123 (at page 5, lines 14-22, for example). In addition, all patients with HER2+ MBC eventually progress despite receiving HERCEPTIN® and thus require alternative therapies.

11. Clinical experience and clinical studies now indicate the existence of at least two populations of patients whose cancers overexpress ErbB2 and progress despite HERCEPTIN® treatment: those with primary HERCEPTIN® resistance (best response to prior HERCEPTIN® being progressive disease) and those with acquired HERCEPTIN® resistance (best response having been either tumor shrinkage or prolonged stable disease). There is currently no clear mechanism for HERCEPTIN®-resistance although several have been put forward with varying degrees of supportive clinical evidence. Thus, it is not clear at this time what characteristics, other than response to treatment with HERCEPTIN® alone, distinguish the subpopulations of breast cancer patients.

12. I note, for example, a recent article (Spector et al (2005) Jour. of Clin. Onc. 23(11):2502-2512) that makes the point that HERCEPTIN® non-responding patients continue to express or overexpress ErbB2. The majority of patients entered onto this study had previously received clinical benefit from HERCEPTIN®. The observation that these patients continue to over-express HER2 was important and not expected. Prior to this recent observation, it would not have been obvious to investigate or to determine whether or not a patient fell into that subpopulation of patients. I believe that this recent observation corroborates and supports the usefulness of the methods described in U.S. Patent Application 09/811,123.

13. I believe that clinicians would find information concerning which population a patient fell into to be clinically useful. For example, in determining a treatment regimen for treating patients, I believe it could be clinically useful to know whether the patient was one whose cancer overexpressed ErbB2 yet did not respond, or responded poorly, to anti-ErbB2 antibody treatment; and that it could be clinically useful to know whether or not the patient had a cancer that overexpressed ErbB2 and did respond to anti-ErbB2 antibody treatment.

14. I believe that it would be helpful in my clinical practice to have available treatment methods to help those patients whose cancers overexpress ErbB2 yet who do not seem to be helped by anti-ErbB antibody treatment.

15. I do not believe that cancer patients with a cancer that overexpresses ErbB2 have yet been treated with anti-ErbB antibody-Maytansinoid conjugates. However, clinical studies with anti-ErbB2 antibody-Maytansinoid conjugates are scheduled to start in early 2006. This drug will be studied in patients with HER2+ metastatic breast cancer who have progressed on or shortly after stopping HERCEPTIN®. The initial studies will administer the drug every 3 weeks for an assessment of toxicity and to identify the correct dose for further studies.

16. Genentech has performed *in vitro* and *in vivo* studies to demonstrate that optimal activity of the conjugate requires high HER2 expression. Genentech has also studied the conjugate in two models of HERCEPTIN®-resistant HER2+ breast cancer and has demonstrated significant activity. These preclinical studies and the recent knowledge that tumors maintain high HER2 expression despite progressing on HERCEPTIN® provide a strong rationale for developing the conjugate in the indicated patient group. As I noted above, recent clinical studies have demonstrated that Her2 antigen continues to be over-expressed on the surface of breast cancer cells once the tumor is clinically resistant to HERCEPTIN®. I believe that this new data is important because it provides an additional rationale for treating this separate, identified patient population with the conjugate targeted to the Her2 antigen.

17. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Date: 9-1-05

Stuart Lutzker, M.D., Ph.D.
Walnut Creek, California

Re: United States Patent Application No. 09/811,123
Filed: March 16, 2001
Title: Methods of Treatment Using Anti-ErbB Antibody-Maytansinoid Conjugates
Inventors: ERICKSON et al.

DECLARATION

I, Mark X. Sliwkowski of San Carlos, California, do declare that:

1. I am an inventor of United States Patent Application Serial No. 09/811,123 of Erickson et al.

2. I have over 14 years of experience in cancer biology research at Genentech, Inc., including research on drugs directed against the human epidermal growth factor receptor family (also known as the HER or ErbB family). Two of these drugs, HERCEPTIN® (Trastuzumab) and Tarceva® (erlotinib) have received U.S. Food and Drug Administration approval. I am currently employed as Director, Staff Scientist: Translational Oncology at Genentech, Inc., and have previously served as a Staff Scientist, at Triton Biosciences, Inc. (Berlex Biosciences, Inc.) from 1985-1991, and as a Staff Fellow at National Institutes of Health, National Heart, Lung and Blood Institute, Laboratory of Biochemistry (1982-1985). I received a Ph.D. degree in Biochemistry from North Carolina State University in 1981. I received the 2005 Pharma Achievement Award as Industry Scientist of the Year. I am an author on many published scientific articles related to my work, have published many abstracts and presented my work at numerous scientific meetings, and am an inventor on several patents. Some of my published articles related to breast cancer and the ErbB receptor are listed in Appendix 1 herein.

3. I have read and am familiar with the specification and pending claims of the United States patent application entitled METHODS OF TREATMENT USING ANTI-ErbB ANTIBODY-MAYTANSINOID CONJUGATES, Serial No. 09/811,123 to Erickson et al.

4. As the Research Project Team Leader and then later the Early Development Team Leader at Genentech, I was responsible for planning, gathering and coordinating the scientific work related to antibody drug conjugates, including the anti-ErbB antibody-maytansinoid conjugate known as trastuzumab-SMCC-DM1. I have worked with other scientists and research associates who are engaged in research in these and in related fields and have observed their level of skill. Based on my education, training, and extensive experience as a scientist in academic and industrial laboratories, I have direct knowledge of the skills and techniques available to one of ordinary skill in the art in the fields related to antibody treatments for cancer, and to antibody-drug conjugates.

5. It is my considered opinion, based on my experience as a research scientist, that the level of skill in the relevant art is very high, most researchers in the area of antibody conjugation research having advanced degrees, and most having extensive laboratory training and experience.

6. I have read and am familiar with the specification and pending claims of the present application. Based on my training and experience, I am familiar with scientific fields related to antibody treatments for cancer, and to antibody-drug conjugates.

7. I note that some of the methods for identifying ErbB-expressing cells to which anti-ErbB antibodies bind were disclosed in the specification of the subject application at pages 58-60 (paragraphs [0211] - [0221] US 2002/0001587). Methods for identifying the target population of patients with ErbB overexpressing tumors were disclosed in the specification of the subject application. For example, the specification at page 60 (paragraph [0224] US 2002/0001587)discusses identification of such patients by an ordinary skilled physician.

8. I am aware of experimental results providing measurements of expression of ErbB and identifying tumor cells which respond to anti-ErbB antibodies. The dynamic range of ErbB2 or HER2 overexpression spans about two orders of magnitude. Normal breast epithelial cells express HER2 at ~10,000 receptors per cell. In contrast tumors that contain HER2 gene amplification may have 1,000,000 HER2 receptors per cell. Using a panel of human breast cancer cell lines, G.D. Lewis et al. (1993) Cancer Immunol Immunother 37:255 demonstrated that the cytostatic effects of HER2 antibodies correlated with HER2 expression level. A threshold of HER2 overexpression was required in order to see cytostasis. This threshold is now thought to be ~100,000 HER2 receptors per cell.

9. As noted in the aforementioned Lewis publication, growth of the breast cancer cell lines SK-BR-3, BT474, MDA-MB-453, MDA-MB-361 is inhibited by certain HER2 antibodies. Thus, these cell lines are some of the cell lines which respond to anti-ErbB antibodies (population A).

10. Many such cancer cell lines which respond to anti-ErbB antibodies (population A) exist and have been studied as xenograft tumors in mice, such as Calu3 xenograft tumors in SCID-beige mice (see attached graph of mean tumor volume progression after IV dosing, Appendix 2, Figure 1). The Calu3 tumors respond well to the anti-ErbB antibody trastuzumab (HERCEPTIN®) with partial remission of 8 of 9 tumor-bearing mice after dosing at 31 mg/kg every 3 weeks. The effects of treatment with naked, unconjugated anti-ErbB antibodies are cytostasis, but not cell death or cytotoxicity.

11. Some population A cell lines or tumors have also been treated with anti-ErbB antibody-maytansinoid conjugates. Complete remission of 8 of 9 Calu3 xenograft tumor bearing mice was observed in the groups dosed with 500 and 1500 $\mu g/m^2$ of trastuzumab-SMCC-DM1 every three weeks (see Appendix 2, Figure 1). In mice, a dose

of 500 μg/m^2 is equal to 165 μg/kg. The effect of treatment of Calu3 xenograft tumor bearing SCID-beige mice resulted in cell death, i.e. cytotoxicity.

12. These experiments can be described as follows. Briefly, Calu3 cells are placed subcutaneously in the flank of immune deficient mice. Depending on the cell line and other conditions, palpable tumors will generally appear within 21 days or so. A tumor of 100 mm^3 is generally thought to be 'established'. Once a sufficient number of mice harbor these established tumors, they are randomized to various number of treatment groups. A typical experiment may have 8 treatment groups with 8-10 animals per group. Randomization ensures that each group has on average the same tumor volume. One or more groups are generally assigned as 'control' groups to internally calibrate therapeutic effects of test agents. Examples of controls might be a vehicle or excipient or a non-specific isotype control antibody. A treatment dose and regimen is pre-determined for each experiment and experimental agent. The therapeutic effect of the test agent is assessed by measuring tumor volumes on a weekly or more frequent basis. The toxicity of the test agent is assessed by measuring body weight, specific stress or damage enzymes in the serum of these animals, cellular blood components and general health of the animals.

13. In addition, we have conducted many experiments which identify cells or tumors which do not respond, or respond only poorly, to anti-ErbB antibodies (population B). This is the basis of the entire research program. Cell lines for *in vitro* proliferation studies and cell lines for xenograft tumor models were selected to set a very high bar for potency, i.e. where the cells do not respond, or respond only poorly, to unconjugated anti-ErbB antibodies.

14. For example, another cell line, BT474E1, in a xenograft tumor in beige nude mice, responded poorly to dosing of trastuzumab at 15 mg/kg every 3 weeks (Appendix 2). Tumors progressed in mice treated with trastuzumab at approximately the same rate as mice treated with the buffer vehicle (placebo).

15. We have also treated cell lines, or tumors of cells which do not respond, or respond only poorly, to anti-ErbB antibodies (population B) with anti-ErbB antibody-Maytansinoid conjugates. These experiments were as described for the Calu3 tumors, except that BT474EI cells are used. The effects of treating some population B xenograft tumor animals and cancer cell lines with anti-ErbB antibody-maytansinoid conjugates are striking. For example, partial and complete remission of BT474E1 xenograft tumor bearing mice was observed in the groups dosed with 150, 500, and 750 μg/m2 of trastuzumab-SMCC-DM1 every three weeks (see graph included here). A dose dependent effect was observed. The effect of treatment of BT474E1 xenograft tumor bearing mice resulted in cell death, i.e. cytotoxicity.

16. There are differences in the responses to anti-ErbB antibody-maytansinoid conjugates between cells, cell lines or tumors of population A and population B, in that all the ErbB expressing cells respond to anti-ErbB antibody-maytansinoid conjugates, but only some ErbB expressing cells respond to unconjugated anti-ErbB antibodies.

17. Based on my experience in conducting research and working with scientists in cancer research over more than fourteen years, and based on my familiarity with the specification of the present application, I believe that the specification provides sufficiently detailed instructions so as to allow a scientist of ordinary skill to determine cells and tumors which overexpress ErbB2 receptor and which do not respond, or respond poorly to treatment with an anti-ErbB2 antibody, and how to treat such cells or tumors with anti-ErbB antibody-maytansinoid conjugates.

18. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the application thereon.

Date: Sept 2, 2005

Mark X. Sliwkowski, Ph.D.
San Carlos, California

Appendix 1:

Franklin MC, Carey KD, Vajdos FF, Leahy DJ, de Vos AM, Sliwkowski MX. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell* 2004 Apr; 5(4): 317-28.

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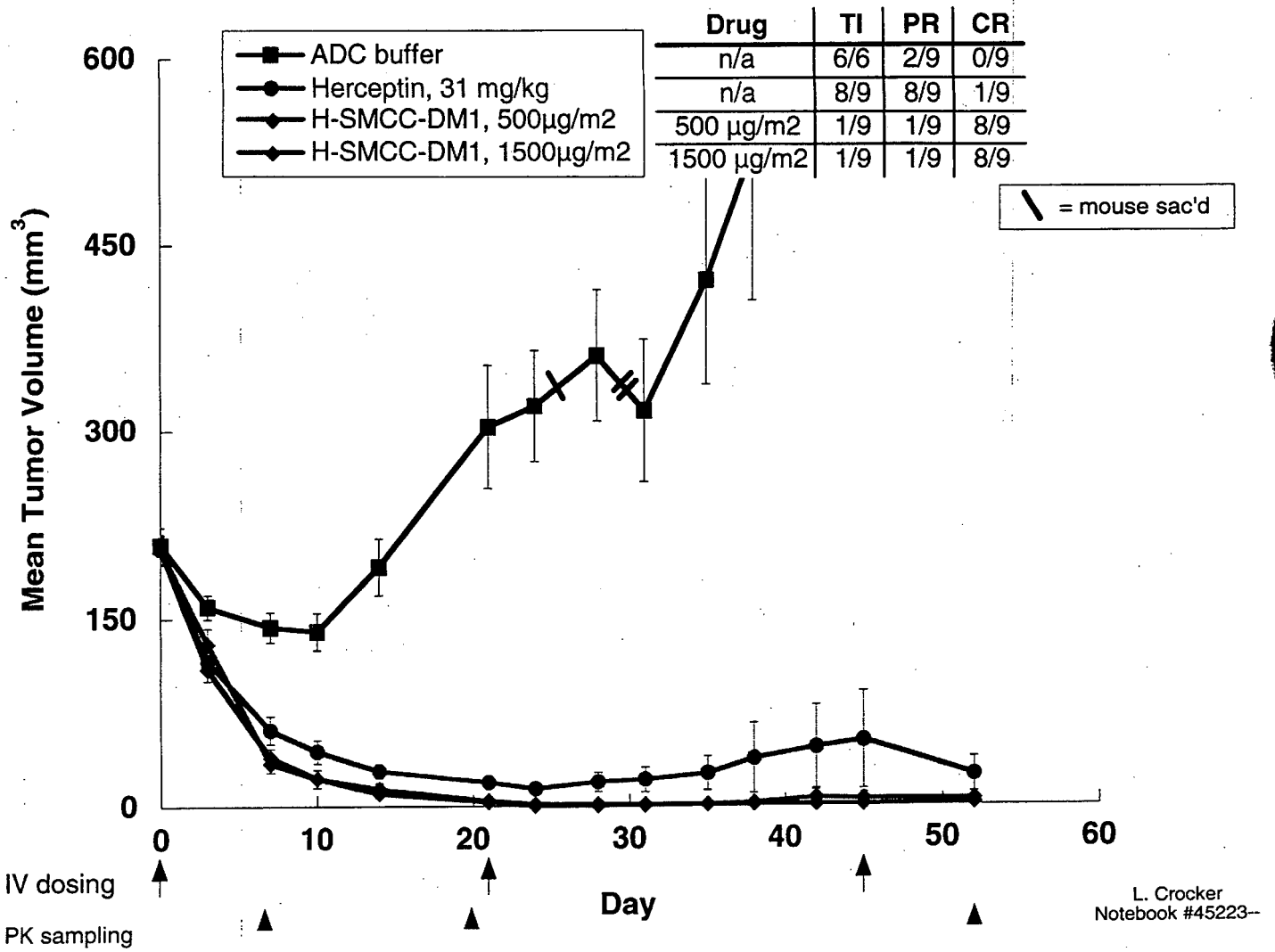
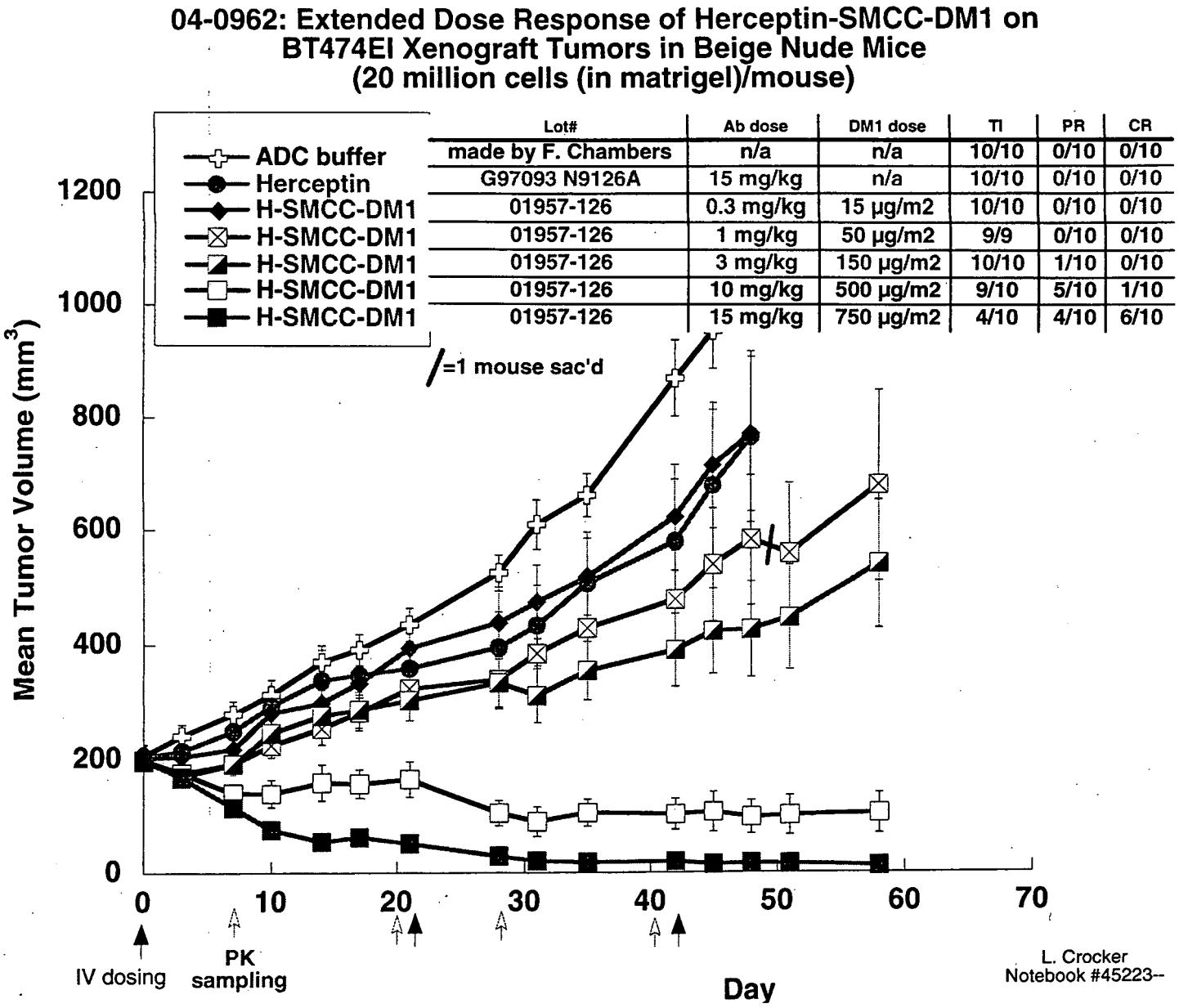
04-0061A: Efficacy of Herceptin-SMCC-DM1 vs. Calu3 Xenograft Tumors in SCID-beige Mice (10 million cells/mouse)



Drug	TI	PR	CR
n/a	6/6	2/9	0/9
n/a	8/9	8/9	1/9
500 µg/m2	1/9	1/9	8/9
1500 µg/m2	1/9	1/9	8/9

L. Crocker
Notebook #45223--

Appendix 2, Figure 1



Lot#	Ab dose	DM1 dose	TI	PR	CR
made by F. Chambers	n/a	n/a	10/10	0/10	0/10
G97093 N9126A	15 mg/kg	n/a	10/10	0/10	0/10
01957-126	0.3 mg/kg	15 µg/m2	10/10	0/10	0/10
01957-126	1 mg/kg	50 µg/m2	9/9	0/10	0/10
01957-126	3 mg/kg	150 µg/m2	10/10	1/10	0/10
01957-126	10 mg/kg	500 µg/m2	9/10	5/10	1/10
01957-126	15 mg/kg	750 µg/m2	4/10	4/10	6/10

Appendix 2, Figure 2